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The Hypertriglyceridemias: Risk and Management

THE INTERNATIONAL COMMITTEE FOR THE EVALUATION
OF HYPERTRIGLYCERIDEMIA AS A VASCULAR RISK FACTOR

Chairs:
Gerd Assmann, MD
Antonio M. Gotto, Jr., MD
Rodolfo Paoletti, MD

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International Committee for the Evaluation of

HYPERTRIGLYCERIDEMIA AS A VASCULAR RISK FACTOR

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Dear Colleague:

Over the past three decades, great progress has been made in identifying and correcting the primary risk factors for cardiovascular disease (CVD), such as smoking, high blood pressure, and elevated total and low-density-lipoprotein cholesterol. In several countries, this has led to a significant reduction in the incidence of CVD.

Despite this encouraging result, CVD is still the leading cause of death in many Western nations. A further decline in cardiovascular morbidity and mortality could be achieved by a wider, multiple-risk-factor approach, with attention paid to lipid risk factors other than hypercholesterolemia. Elevated plasma triglycerides, often associated with low high-density-lipoprotein cholesterol levels, may play a significant role in cardiovascular risk.

Hypertriglyceridemia as a risk factor for CVD has been evaluated by an international committee, established by the Giovanni Lorenzini Medical Foundation. This supplement to the *American Journal of Cardiology* summarizes the findings of this committee.

This review covers the most recent experimental and clinical findings on the pathophysiology of triglyceride transport, the epidemiologic evidence on the role of triglycerides in CVD, and the laboratory procedures for diagnosing disorders of the triglyceride-carrying lipoproteins. Particular attention has been paid both to the identification of hypertriglyceridemic patients at particular risk for CVD and to their management, whether by drugs, diet, or other nonpharmacologic approaches.

The present document is intended as a position paper for stimulating discussion on the role of triglycerides in CVD and to aid the physician in assessing the significance of triglyceride elevations.

Gerd Assmann   Rodolfo Paoletti

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Introduction

G. Assmann, MD, A.M. Gotto, Jr., MD, and R. Paoletti, MD

Great progress has been made over the past 30 years in identifying the risk factors of cardiovascular disease (CVD) and in decreasing the incidence of CVD through the treatment of risk factors.

In the 1960s, for example, physicians began endorsing smoking cessation as a preventive measure against both CVD and lung cancer. In the 1970s the United States National High Blood Pressure Education Program led a campaign against hypertension, setting guidelines for its proper diagnosis and management. In the 1980s the focus shifted to the diagnosis and management of hypercholesterolemia, with cholesterol-control guidelines developed in the United States, Canada, Europe, and Japan. The identification and proper management of these three risk factors are widely believed to have contributed importantly to the declining rates of CVD mortality throughout the industrialized world. In the United States alone, the annual rate of CVD mortality dropped by approximately 25% from 1968 to 1987.[1]

But despite these encouraging results, CVD is still the largest killer in many of the industrialized nations, including the United States. For example, even with the downturn in CVD mortality since the 1960s, the U.S. Department of Health Statistics predicts that CVD will cause the deaths of approximately 1 million U.S. citizens in 1991.[2]

A further decline in cardiovascular mortality could likely be achieved by full implementation of the guidelines of the various national organizations. For example, existing evidence in the United States indicates that considerably more risk-factor modification has occurred in groups at higher socioeconomic levels. Furthermore, prevention strategies, which in the past may have been narrowly focused on one or two CVD risk factors, should now be formulated to take on a wider, multiple-risk-factor approach. Treatments that may have improved one risk factor profile while worsening another should be taken into account when several risk factors coexist, for example, hypertension, hyperlipidemia, and diabetes.

The purpose of this review is to summarize existing evidence concerning hypertriglyceridemia and coronary heart disease (CHD). We should begin by stating that the scientific basis relating elevated serum triglycerides to CHD is not as strong as for low-density lipoprotein (LDL) cholesterol. Many studies have shown a positive correlation between elevated serum triglyceride levels and increased CHD risk,[3–6] in both men and women and particularly in patients with non-insulin-dependent diabetes.[3,7–16] Also, patients with angiographically documented CHD[17–20] and survivors of myocardial infarction[5,21–22] have hypertriglyceridemia much more frequently than unaffected individuals.

However, the "independence" of the relationship between elevated serum triglyceride levels and CHD remains an issue of debate. Part of the controversy stems from the fact that—unlike total serum cholesterol, LDL cholesterol, and high-density lipoprotein (HDL) cholesterol—triglycerides do not appear to have a continuous or stepwise relationship to CHD risk. Also, the independent link between elevated serum triglycerides and CHD breaks down when multivariate analyses are used to control statistically for the effects of total cholesterol and HDL cholesterol.[9,21,23–26] These qualifications suggest that the increased CHD risk noted in patients with hypertriglyceridemia could be due either to the accumulation of triglyceride-rich particles that are uniquely atherogenic in only some people or to the association with other risk factors, such as reduced levels of HDL cholesterol.[27]

The atherogenic potential of the triglyceride-rich lipoproteins (TGRL) is supported by the following evidence. First, TGRL levels have a strong influence on HDL-cholesterol concentrations,[28] and even if a low HDL level is atherogenic, the primary cause may be elevated triglycerides.

This link has been clearly documented in the postprandial state, when the entry of chylomicrons into the circulation challenges an individual's fat-clearing capacity.[29] In other words, patients with low HDL levels often show an exaggerated postprandial lipemia. Secondly, several investigators have suggested that a delayed clearance of dietary fat, i.e., an extended postprandial lipemia, may induce the uptake of triglyceride-rich remnants by arterial cells,[30,31] resulting in an intracellular accumulation of cholesteryl esters and in the subsequent development of atherogenic foam cells.[32–35] Very-low-density lipoprotein (VLDL) remnants may also be atherogenic, as illustrated by the increased CHD risk accompanying familial dysbetalipoproteinemia.

The committee recognizes that the foundation of the lipid hypothesis rests on the link between cholesterol and CHD and that the existing body of scientific evidence concerning triglycerides is still insufficient to support the promulgation of a comprehensive set of guidelines for triglyceride lowering in the general population. Further, for the scientific community, LDL is the key atherogenic lipoprotein, and priority has appropriately been given to recommendations for modifications and management of elevated LDL levels (see National Cholesterol Education Program and European Atherosclerosis Society guidelines). This committee recognizes and endorses these strategies. The purpose of this report is *not* to oppose the focus on cholesterol and LDL as the major lipid determinants of atherosclerosis, but is rather to complement it by paying attention to the growing evidence that triglyceride-rich lipoproteins also have atherogenic potential, and in some patients deserve attention. In our opinion, if we are to take advantage fully of all the information provided in the analysis of lipids and lipoproteins, we must consider how best to approach abnormalities in serum triglycerides.

The committee further notes that in the United States an increasing number of people enter the cholesterol management algorithm with a lipoprotein analysis—total cholesterol, triglycerides, HDL cholesterol, and estimated LDL cholesterol—and not with a total cholesterol measurement alone. Some of these people will have elevations of LDL cholesterol and can readily enter the scheme for their management, as recommended by the National Cholesterol Education Program guidelines. Others will have desirable levels for LDL cholesterol, but abnormalities in triglycerides and/or HDL. This document pays special attention to those of the latter group who manifest hypertriglyceridemia. In doing so, it does not negate the National Cholesterol Education Program guidelines for treatment of high LDL cholesterol, but instead offers suggestions for the management of hypertriglyceridemic states that fall outside the conditions subsumed by these guidelines. In Europe, management of hypertriglyceridemia is an integral part of European Atherosclerosis Society policy statements. This report updates the most recent developments and specifies in more details the recommended actions in this area. Thus, it should assist physicians in the treatment of patients for whom such detailed guidelines have not been made available. The main points of the new suggestions are summarized below:

Clinically Significant Action Limits for Fasting Triglyceride (TG) Levels

- TG >200 mg/dL (>2.3 mmol/L) deserve attention.
- TG between 200–400 mg/dL (2.3–4.5 mmol/L) are regarded as moderately elevated. A more precise classification of lipid abnormality requires information on LDL-cholesterol and HDL-cholesterol. "Mixed lipid disorders" (moderately elevated TG + high LDL-cholesterol or low HDL-cholesterol) require more aggressive management.
- TG >1000 mg/dL (>11.2 mmol/L) raise the risk of pancreatitis.

On this basis, the committee proposes the following stepwise approach (see Chapter 7A) to the treatment of patients with elevated triglycerides:

1. Identify the cause for the elevated triglycerides. Triglyceride levels should always be analyzed after an overnight fast and at least two or three measurements should be made prior to the diagnosis and determination of treatment. Hypertriglyceridemia can be of genetic origin or acquired. Hypertriglyceridemia can thus be a signal for a not yet diagnosed disease or for a familial disposition of concern. Frequently, life-style changes, a change in co-medication, or the treatment of underlying diseases correct the elevated triglyceride levels.

2. Identify the overall risk pattern of the patient. Attention to all the modifiable risk factors is appropriate. An effort should be made to identify and control secondary causes of hypertriglyceridemia, such as diabetes mellitus, renal disease, and use of drugs. Smoking and hypertension should be vigorously controlled. The identification of other genetic forms of hyperlipidemia, such as familial combined hyperlipidemia and type III hyperlipidemia, is important. Accompanying elevations of LDL cholesterol, low levels of HDL cholesterol

TABLE I Major CHD Risk Factors

- Elevated LDL-cholesterol
- Male sex
- Family history of premature CHD (definite myocardial infarction or sudden death before 55 years of age in a parent or sibling)
- Cigarette smoking (currently smokes more than 10 cigarettes per day)
- Hypertension
- Low HDL-cholesterol concentration (below 35 mg/dL confirmed by repeated measurement)
- Diabetes mellitus
- History of definite cerebrovascular or occlusive peripheral vascular disease
- Severe obesity (≥30% overweight)

(<35 mg/dL), and a personal or family history of CHD are addressed by the current guidelines. The clustering of risk factors leads to more than an additive increase of cardiovascular risk.

3. Treat patients with an overall risk pattern.
Moderate levels of several risk factors (Table I) justify medical attention as much as a strongly elevated individual factor.

4. Diet is the first-line treatment for hypertriglyceridemia.
Weight reduction (when needed) and a diet low in saturated fats and cholesterol are of primary importance. Exercise also improves the overall cardiac profile. Alcohol restriction is mandatory.

5. Drug therapy may be considered if diet is ineffective, although this remains controversial.
Some groups of patients with hypertriglyceridemia may be considered for drug treatment if diet is ineffective. While there is general consensus that treatment of TG levels greater than 1,000 mg/dL reduces the risk of pancreatitis, the use of drugs to reduce CHD risk is controversial; the efficacy of reducing triglycerides to decrease CHD has not been yet conclusively established.

Fibrates and nicotinic acid are the first-line drugs for hypertriglyceridemia. The HMG-CoA reductase inhibitors have a moderate effect on reducing triglycerides, in the order of 15–20%. A statin might be considered for a patient who had primary hypercholesterolemia with mild accompanying hypertriglyceridemia.

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1. Pathophysiology of Triglyceride-Rich Particles

A. METABOLISM OF TRIGLYCERIDE-RICH PARTICLES

J. Shepherd, MD, and R.M. Krauss, MD (Reviewer)

The first reason why we cannot ignore the impact of elevated serum triglyceride levels on cardiovascular disease (CVD) risk is because of the close relationship between the metabolism of triglyceride-rich particles, such as chylomicrons and very-low-density lipoproteins (VLDL), with that of high-density lipoproteins (HDL). Indeed, an individual's ability to metabolize triglyceride has a profound effect on the structure, metabolism, and function of low-density lipoproteins (LDL) and HDL, due, in part, to interparticle lipid exchange. This section will provide a brief review of the pathophysiology of triglyceride-rich particles.

Following its absorption in the intestine, dietary fat is packaged into large triglyceride-rich chylomicron particles (Figure 1), which contain a number of surface proteins, called apolipoproteins (apo A-I, A-IV, and B-48). The secretion of these particles is critically dependent on the production of apo B.

Apo B is formed in the liver and intestine. In the liver the apo B gene is fully expressed and generates a 5,235 amino acid product known as apo B-100. In the intestine, however, a unique mRNA editing process[1] introduces a stop codon (a CAA →UAA conversion) at the gene's 2,152 amino acid. The stop codon truncates the apo B product into a smaller protein known as apo B-48. The full biologic benefits of this truncating process are not known. But one benefit appears to be that particles containing apo B-48, including some triglyceride-carrying chylomicrons, are not able to bind to LDL receptors and are directed instead to alternative degradative pathways. Apo E appears to play an important part in this process.

After their secretion, the chylomicrons acquire the apo Cs and apo E from HDL particles. Acquired apo C-II modulates the hydrolysis of the chylomicron by acting as a cofactor for the enzyme lipoprotein lipase. This enzyme, located on capillary endothelial surfaces in skeletal muscle and adipose tissue,[2] catalyzes the hydrolysis of triglyceride from the chylomicron core, releasing fatty acids for storage or energy requirements. The chylomicron itself shrinks progressively, shedding its surface phospholipid and small molecular weight proteins into nascent HDL particles. The remaining chylomicron remnant is then cleared rapidly by the parenchymal cells of the liver. These cells possess an LDL receptor-related protein (LRP or chylomicron remnant receptor), which binds to the apo E and might be a candidate for the putative chylomicron remnant receptor.[3] The present role of apo C-III is not clearly defined; it may delay apo E–mediated VLDL uptake until the triglyceride hydrolysis is completed.

Once absorbed into the liver, the lipid component of the chylomicron remnant is either stored, catabolized, or resecreted as a component of endogenous lipoproteins, such as triglyceride-rich VLDL particles. VLDL particles—which contain apo B-100, the apo Cs, and apo E—are subject to the same hydrolytic process as the chylomicrons, namely, the lipolysis of their triglyceride core by the lipoprotein lipase enzyme. The remaining VLDL remnant, known as intermediate-density lipoprotein (IDL), is relatively rich in cholesteryl ester. In normal individuals, a portion of IDL is cleared directly by the liver through the binding of apo E. Another portion is hydrolyzed further into LDL particles, the major cholesterol transporters in human plasma.

Studies of human lipase deficiency syndromes have shown that the lipolysis of large triglyceride-rich VLDL to smaller remnants is dependent entirely on the activity of lipoprotein lipase. In contrast, the conversion of IDL to LDL involves the action of hepatic lipase, a second enzyme located on the membrane of liver parenchymal cells. These two enzymes, from distinct but related genes, are particularly important in modulating triglyceride transport through the plasma and in influencing the structure and serum concentrations of the denser cholesterol-rich LDL and HDL lipoproteins.

Individuals with high lipoprotein lipase activity (for example, young females or athletes) tend to have low VLDL–triglyceride concentrations and high HDL (particularly HDL_2) concentrations. Conversely, individuals with higher hepatic lipase activity (men and individuals taking anabolic steroids) have low HDL levels. The probable explanations for these correlations, including the role of postprandial lipemia,[4] will be discussed in a later section (see Chapter 2). But we can point out here that the ratio of lipoprotein/hepatic lipase activity may offer a strong indication of an individual's atherosclerosis risk.

The important role played by hepatic lipase in the metabolism of LDL and HDL is clearly evident in individuals hereditarily deficient in this enzyme.[5] These individuals accumulate IDL and HDL_2 particles. Moreover, their HDL_2 particles are large and triglyceride-rich, reflecting their continuous acquisition of triglyceride from VLDL in exchange for cholesteryl ester. This exchange is mediated by the cholesteryl ester transfer protein. Normally, the effects of the cholesteryl ester transfer protein are balanced (Figure 1) by the action of hepatic lipase; the latter catalyzes the hydrolysis of triglyceride present in HDL_2 to produce smaller and denser HDL_3 particles. Individuals who lack either the cholesteryl ester transfer protein gene[6] or are completely deficient in triglyceride-rich particles[7] (i.e., are abetalipoproteinemic) accumulate cholesteryl ester–enriched HDL_2 and larger apo E–rich HDL_1 particles; these latter display a much higher affinity than LDL in binding to the LDL receptor.

The VLDL metabolized by the liver vary in size and composition, depending on their relative proportions of lipids and apolipoproteins. Kinetic studies[8] have shown that large VLDL are converted virtually quantitatively into smaller remnant particles that are cleared directly from the circulation without contributing to the LDL pool. In contrast, smaller, cholesterol-enriched VLDL particles are rapidly converted into LDL and constitute the main source of the LDL pool.

Lipase deficiencies severely disrupt the normal metabolism of triglyceride-rich particles. Less dramatic disruptions, however, are also seen in familial hypercholesterolemic subjects, who lack the classic LDL receptor, and in type III hyperlipoproteinemic individuals, who have inherited a mutated apo E that does not bind readily with its receptor. In both of these conditions, remnants rich in cholesteryl ester accumulate in plasma, while the conversion of IDL to LDL is inhibited. Moreover, both conditions are associated with an increased risk of CVD.

This increased risk prompts the speculation that particular subclasses of triglyceride-rich lipoproteins predispose to atherosclerosis. Such a theory is

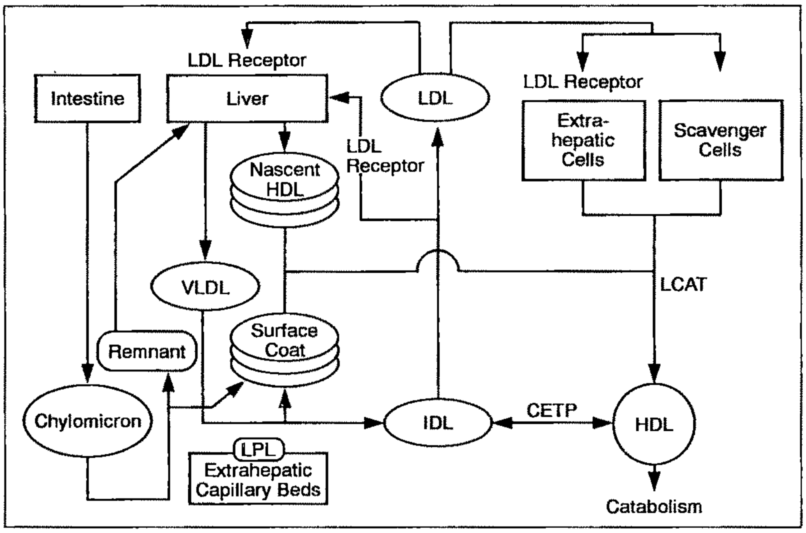

FIGURE 1. Lipoprotein metabolism. Following its absorption, dietary fat is packaged into large triglyceride-rich chylomicron particles within the enterocyte and secreted into the circulation. There, lipolysis reduces the particle's triglyceride core and makes redundant part of its surface coat, which is shed to high-density lipoprotein (HDL). The remnants produced in the process are rapidly assimilated by a receptor-mediated mechanism in the liver. In the fasting state, very-low-density lipoprotein (VLDL) replaces chylomicron as the major triglyceride transporter, and the liver dominates lipoprotein metabolism. Cholesterol and triglyceride elaborated in this organ are released into the plasma. In the plasma, they become subject to tissue lipolysis, which degrades them to low-density lipoproteins (LDL) via an intermediate species called intermediate density lipoproteins (IDL). The LDL is removed by receptors present on liver and peripheral tissues. When these are saturated, an alternative, scavenger pathway becomes dominant. Interchanges of lipids between circulating lipoprotein particles is facilitated by the plasma enzyme lecithin:cholesterol acyltransferase and cholesteryl ester transfer protein (CETP), both of which participate in the process of reverse cholesterol transport from peripheral sites to the liver, where the sterol is excreted.

lent credence by the fact that triglyceride-rich remnant particles are the only naturally occurring plasma lipoproteins that can induce cholesteryl ester accumulation in cultured macrophages.[9]

Triglyceride-rich particles may also contribute directly to the atherogenic process through their absorption by macrophage receptors, which recognize and bind to peroxidized lipoproteins.[10] Several studies have shown that macrophages bind and internalize triglyceride-rich particles in proportion to their apo E content.[11] But more recent studies have also shown that the macrophages possess on their membranes a binding domain that does not require apo E but, instead, appears to recognize peroxidized lipoproteins.[10] Assimilation of these species stimulates cholesterol esterification at twice the rate seen during the uptake of unoxidized lipoproteins.

Although the above data suggest a direct role for triglyceride-rich lipoproteins in the pathogenesis of atherosclerosis, these lipoproteins may also influence atherosclerotic risk, and subsequently CVD risk, in more subtle, indirect ways.[12]

One example involves the cholesteryl ester transfer protein. The cholesteryl ester transfer protein, which promotes the rapid molecular exchange of cholesteryl ester for triglyceride between all serum lipoprotein species, is more active in individuals with sustained hypertriglyceridemia. When triglyceride-rich lipoproteins are present in excess, the cholesteryl ester transfer protein promotes the triglyceride enrichment of HDL, with concomitant cholesteryl ester accumulation in VLDL. VLDL particles enriched in cholesteryl ester may then promote the delivery of cholesteryl ester to macrophages, while triglyceride-enriched HDL particles are good substrates for the hepatic lipase enzyme. The enzyme transforms these large HDLs into smaller, more dense species that are cleared more rapidly from the bloodstream. The net effects are an increased accumulation of cholesteryl ester in the macrophages and a lower level of HDL, which, in turn, compromises the process of reverse cholesterol transport.

A similar phenomenon occurs within the LDL density spectrum. Here, higher plasma triglyceride levels skew the distribution of LDL particles toward smaller, more dense species. Epidemiologic studies have indicated that the smaller species are linked to an increased CVD risk.[13,14] Indeed, there appears to be a risk syndrome, common in the population, which is characterized by the constellation of moderate hypertriglyceridemia, low HDL_2 and small, dense LDL.[14,15]

CONCLUSION

Numerous studies on the pathophysiology of triglyceride-rich particles have shown that some of these particles make both direct and indirect contributions to the atherogenic process. Therefore, measuring triglycerides can provide important information for the assessment of coronary risk.

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1. Pathophysiology of Triglyceride-Rich Particles

B. TRIGLYCERIDE-RICH LIPOPROTEIN CELL INTERACTIONS

Y. Stein, MD, and R.J. Havel, MD (Reviewer)

The intent of this section is to provide a selective, not exhaustive, review of triglyceride-rich lipoprotein metabolism studies in cell cultures. This section will also examine the interaction of these lipoproteins with cellular receptors in other systems.

STUDIES WITH CHYLOMICRONS AND VERY-LOW-DENSITY LIPOPROTEINS (VLDL)

VLDL are heterogeneous particles with respect to their size and composition of lipids and apoproteins.[1,2] Gianturco et al. have shown that large VLDL (Sf 60–400) from subjects with endogenous or mixed hypertriglyceridemia bind at least as effectively as normal low-density lipoproteins (LDL) to the LDL receptor of human skin fibroblasts, while smaller VLDL from normotriglyceridemic subjects bind little or not at all.[3] The explanation is apparently that apo E, not apo B-100, is the binding determinant for the larger hypertriglyceridemic VLDL.[4,5] Indeed, the receptor binding determinant for hypertriglyceridemic VLDL switches from apo E to apo B-100 as VLDL of Sf 20–60 convert into intermediate-density lipoproteins (IDL) and LDL.

It is not clear whether a relative lack of apo E on the large surface of some VLDL particles, or the putative loss of apo E that occurs during the isolation of VLDL by ultracentrifugation, is the reason for the poor interaction of some VLDL particles with the LDL receptor. Eisenberg et al. have shown that all VLDL fractions are able to bind apo E. The investigators have also confirmed that the acquisition of apo E increases VLDL interaction with the LDL receptor.[6] Maximal binding of normal VLDL is achieved when the apo E:apo B weight ratio is between 0.3–0.5, corresponding to five to nine molecules of apo E per VLDL particle. However, this apo E concentration is about twice as much as the apo E content in VLDL isolated by ultracentrifugation or separated by gel chromatography.[2] These results, therefore, suggest that an unavailability of apo E in the appropriate conformation may be limiting for optimal binding (and cellular uptake) of VLDL.

VLDL differing in their content of apo E have been separated by electrophoresis,[7] by heparin-affinity chromatography,[8] and by apo E immunoaffinity chromatography.[9]

Studies with normal and hyperlipidemic Watanabe rabbits have shown that some VLDL particles completely lack apo E.[9] These VLDL particles are taken up into the liver via the LDL receptor much less effectively than those VLDL that contain several molecules of apo E. Furthermore, large VLDL that contain apo E are taken up more rapidly than smaller apo E-containing VLDL.[10] Human VLDL particles that lack apo E do not bind to the LDL receptor, indicating that the apo B-100 component of the VLDL is in a receptor-inaccessible conformation.[11] However, once the triglycerides of the VLDL particle have been hydrolyzed by lipoprotein lipase, the apo B component becomes accessible to the receptor.[12]

Recent studies have shown that two types of human VLDL particles lacking apo E can be separated from both normotriglyceridemic and hypertriglyceridemic subjects by combined heparin affinity and anti–apo E immunoaffinity chromatography. Both types of particles have very low affinity for the LDL receptor.[13] In contrast, apo E–containing VLDL bind to the LDL receptor. But, as noted by Gianturco et al.,[3] apo E-containing VLDL from hypertriglyceridemic subjects bind with much higher affinity than those from normotriglyceridemic subjects.

Kowal et al. have recently noted that the effects of apo E on lipid binding extend to the LDL receptor–related protein.[14] In their investigations, the addition of apo E from cholesterol-fed rabbits greatly augmented the binding of rabbit beta-VLDL via the LDL receptor-related protein to human skin fibroblasts from subjects with no LDL receptors.

Using rat VLDL enriched with added C apolipoproteins, Windler et al. showed that the ability of apo E-containing VLDL to bind to the LDL receptor is modulated by the C apolipoproteins.[15] Loss of these apos during the formation of VLDL remnants by lipoprotein lipase evidently contributes to the recognition of the VLDL's remaining apo E component by hepatic LDL receptors.[16]

Chylomicrons, which contain receptor-incompetent apo B-48, but also apo E, do bind to the LDL receptor and, potentially, to the LDL receptor-related protein.[17,18] The binding of chylomicron remnants via apo E is theoretically modulated by the C apolipoproteins,[15] as the case with VLDL. However, there have been no formal chylomicron binding studies to confirm this theory.

STUDIES WITH IDL

The cellular metabolism of human IDL (density = 1.006–1.019 g/mL) has been investigated in human skin fibroblasts and HepG2 cells in the absence and presence of exogenously added apo E.[19] IDL was found to be metabolized to a lesser extent than LDL, but its uptake and degradation was brought to the LDL levels by increasing the complement of apo E from two or three molecules of apo E per particle to four or five molecules per particle.

STUDIES WITH HYPERTRIGLYCERIDEMIC LDL

LDL isolated from hypertriglyceridemic diabetics and from nondiabetic hypertriglyceridemic subjects have shown a reduced cellular binding to human skin fibroblasts.[20–22] In contrast, LDL isolated from normotriglyceridemic diabetics have shown normal binding.[23]

Kleinman et al. found that treatment with bezafibrate normalizes triglyceride levels and raises LDL binding to control levels.[22] The investigators concluded that the reduced LDL binding in hypertriglyceridemic subjects is due to the lower affinity of the apo B component of hypertriglyceridemic LDL for the LDL receptor. This reduced affinity is apparently related either to the smaller size of the LDL particle or to a change in the conformation of the apolipoprotein B, rather than to a change in the LDL's apolipoprotein composition or to an abnormal apo B molecule. However, hypertriglyceridemia evidently confers a conformational change in apo B-100, resulting in its decreased recognition by the LDL receptor.[24]

Finally, three studies have shown that during longer incubation periods of up to 48 hours, hypertriglyceridemic LDL down-regulate the LDL receptors in human skin fibroblasts to a lesser degree than do normal LDL. The resulting larger number of LDL receptors, when extrapolated to in vivo conditions, could explain the shorter half-life of apo B in subjects with hypertriglyceridemia.[25–27]

CONCLUSION

Studies with chylomicrons, VLDL, IDL, LDL, and their metabolic products support that these different particles carry a different atherogenic potential. For example, apo E–containing VLDL from hypertriglyceridemic subjects bind to LDL receptors with much higher affinity than those from normotriglyceridemic subjects. The unique cell interactions associated with hypertriglyceridemia provide further evidence of the close relationship between triglyceride and other lipid metabolism.

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ostprandial Hyperlipidemia

otto Jr., MD, J. Patsch, MD, and A. Yamamoto, MD (Reviewer)

between the metabolism of triglycer- ich lipoproteins and high-density li- protein (HDL) concentrations has been documented in the postprandial state.[1,2] Several investigators have suggested that an extended postprandial lipemia may induce the uptake of triglyceride-rich remnants by arterial cells[3,4] and, thus, increase the atherogenic intracellular accumulation of cholesteryl esters.[5–8] This section will examine the inverse relationship between postprandial triglyceride levels and HDL concentrations and will review the effect of postprandial lipemia on cardiovascular disease (CVD) risk.

METABOLISM OF HDL AND TRIGLYCERIDE-RICH LIPOPROTEINS

HDL particles are secreted as disc-shaped precursors devoid of cholesteryl esters. Through the action of the cholesterol-esterifying plasma enzyme lecithin:cholesterol acyltransferase, the nascent HDL particles are transformed into mature, spherical-shaped HDL. There are two major subfractions of mature HDL: a small, lipid-poor, and dense HDL$_3$ and a larger, more lipid-rich, and less dense HDL$_2$. Most individuals have fairly constant levels of HDL$_3$, while their levels of HDL$_2$ vary widely. The levels of HDL$_2$ may account for the variability of an individual's total HDL-cholesterol level and, subsequently, for the associated coronary heart disease (CHD) risk.

Serum HDL$_2$ levels are inversely correlated with the magnitude of postprandial lipemia.[1,9] The extent of lipemia, in turn, is determined in part by the activity of the enzyme lipoprotein lipase (LPL; see Chapter 1A). Thus, in individuals with high LPL activity and, subsequently, with reduced postprandial lipemia, the rapid lipolysis of triglyceride-rich chylomicrons keeps HDL$_2$ levels high by promoting the formation of the larger HDL$_2$ particles as well as by preventing their catabolism. High levels of HDL$_2$, therefore, reflect an effective catabolism of triglyceride-rich lipoproteins. Conversely, in individuals with low LPL activity and, subsequently, with pronounced postprandial lipemia, the delayed lipolysis of triglyceride-rich chylomicrons reduces HDL$_2$ levels by promoting the formation of HDL$_3$ at the expense of the larger HDL$_2$ particles. Individuals with high levels of HDL$_2$ may be less prone to CHD because of their rapid clearance of triglyceride-rich lipoproteins from the circulation, while individuals with low levels of HDL$_2$ are more prone to CHD because of the accumulation of chylomicrons.

These findings support a so-called "noncausalist" theory regarding HDL-cholesterol and CHD. The theory states that the negative correlation between HDL-cholesterol levels and CHD risk does not depend solely on a direct antiatherogenic action of HDL, commonly associated with the reverse cholesterol transport theory. According to this theory, HDL particles trap excess cholesterol from cellular membranes by esterification and then transfer the esterified cholesterol to triglyceride-rich lipoproteins. The subsequent removal of these lipoproteins by hepatic receptors completes the reverse cholesterol transport.

But according to the "noncausalist" theory, the "protective" effect of elevated HDL levels on CHD risk reflects the inverse correlation between HDL$_2$ levels and postprandial triglyceride levels.[1,9] Rapid clearance of chylomicrons promotes the formation of HDL$_2$, so that a high level of HDL$_2$ (and of total HDL-cholesterol) is a marker for the efficient catabolism of triglyceride-rich lipoproteins. Low levels of triglyceride-rich lipoproteins do not allow the excessive transfer of HDL-cholesteryl esters into the triglyceride-rich remnants. This keeps the cholesteryl esters in HDL. As a result, HDL plasma levels produce an antiatherogenic net effect and are inversely related to CHD.

CLINICAL TRIALS

The "noncausalist" theory described above has gained credence from at least two clinical studies.[9,10] In the first of these studies, patients who underwent coronary arteriography and who also had fasting plasma triglycerides of less than 250 mg/dL were given an 8-hour fat-tolerance test.[9]

The patients with a coronary score of over 50, indicating severe CHD, were then compared with a group of control patients who had coronary scores of 0. A preliminary evaluation of 93 patients from this ongoing study indicated that those patients with severe CHD had higher levels of fasting triglycerides, lower levels of HDL$_2$ cholesterol, and larger magnitudes of postprandial lipemia. Moreover, when compared to all of the conventional lipid parameters for the fasted state, the magnitude of postprandial lipemia—graphically quantified as the area under the postprandial triglyceride curve—was the strongest discriminator between patients with severe CHD and the controls.

Single postprandial triglyceride levels at time points beginning with 6 hours postprandially were also able to discriminate between cases and controls. This finding suggests that only one or two postprandial blood specimens, at 6 and 8 hours postprandially, may have to be taken during an 8-hour fat-load test, a simplification that makes the test more practical for prospective epidemiologic studies.

Similar results were recorded in a second clinical study.[10] In this study, 20 normolipidemic patients with CHD and 20 normal subjects were given oral lipid loads. Blood samples, taken every 2 hours until 14 hours and then after 24 hours, were analyzed for total cholesterol and triglyceride levels. The patients with CHD were found to have delayed chylomicron-remnant removal and lower fasting levels of HDL-cholesterol.

CONCLUSION

Triglycerides should not be prematurely dismissed as a potential important causal risk factor for CHD. There is now a large body of evidence suggesting that the metabolism of triglyceride-rich lipoproteins affec[illegible] of HDL cholesterol; [illegible] are, in part, integrative m[illegible] postprandial triglyceride m[illegible] evaluation of the metabolism [illegible] lipoproteins, when challenged by [illegible] oral fat-load test, may help to disc[illegible] tween patients with and without CHD.

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3. Genetic (Primary) Forms of Hypertriglyceridemia

G. Assmann, MD, and H.B. Brewer, Jr., MD (Reviewer)

Hypertriglyceridemia is often symptomatic of underlying genetic abnormalities of lipid metabolism.

TRIGLYCERIDES AND ATHEROSCLEROSIS

Triglyceride plasma concentrations exceeding 200 mg/dL (2.3 mmol/L) in adults or 140 mg/dL (1.6 mmol/L) in individuals below age 20 are generally termed hypertriglyceridemia. Most epidemiologic studies have failed to identify hypertriglyceridemia as an independent risk factor of atherosclerosis.[1-7] However, more recent analyses of the Framingham study suggest an elevated triglyceride level is an independent risk factor for coronary heart disease (CHD) in both men and women over age 50, when excessive triglycerides coincide with low high-density lipoproteins (HDL) or with an high ratio of plasma cholesterol to HDL.[8] Furthermore, slightly increased levels of triglycerides are often combined with conditions (e.g., diabetes, obesity, alcoholism) that predispose to atherosclerosis and other diseases.

In some patients, hypertriglyceridemia indicates genetic abnormalities of lipoprotein metabolism that lead to premature and severe atherosclerosis. For example, the basic defect in type III hyperlipidemia results in the accumulation of triglyceride-rich remnant particles that play a causative role in the formation of atherosclerosis.[9-11] In families affected with familial combined hyperlipidemia, another high-risk lipid anomaly, subjects with increased triglycerides appear to be at the same coronary risk as those family members with increased cholesterol.[12,13] In contrast, monogenic familial hypertriglyceridemia does not appear to put affected family members at increased risk for myocardial infarction.[14]

This complexity demands a classification of hypertriglyceridemias that will enable clinicians to identify those patients at risk for premature cardiovascular disease and to decide which patients require therapeutic interventions. This section will describe the genetic anomalies causing hypertriglyceridemia.

GENETIC ANOMALIES IN THE METABOLISM OF TRIGLYERCIDES

A. Genetic anomalies of chylomicron and very-low-density lipoprotein (VLDL) assembly: Plasma apo B is present in humans as apo B-48 and apo B-100. The two apo B isoproteins are synthesized by a unique editing mechanism of apo B mRNA[15] (see Chapter 1A). Apo B-100, the apo B isoprotein present in low-density lipoproteins (LDL), is secreted by the liver as VLDL. Lipoproteins synthesized by the intestine contain predominantly apo B-48; a relatively small number of particles (15%) may contain apo B-100.[16] Lipoproteins containing apo B-100, but not apo B-48, are thought to be important in the development of premature cardiovascular disease.

The relative proportion of apo B-48 and atherogenic apo B-100 lipoproteins synthesized by the intestine may be potentially modulated by diet, hormones, and drugs. Patients with genetic defects in the editing process would be unable to edit the apo B mRNA and would switch from the synthesis of apo B-48 to apo B-100 lipoproteins; thus the intestine would become a major synthesis site of atherogenic lipoproteins.

B. Genetic anomalies of lipoprotein lipase and apo C-II: The effective hydrolysis of plasma triglycerides requires lipoprotein lipase and its cofactor apo C-II. Genetic defects in either lipoprotein lipase or apo C-II result in defective triglyceride hydrolysis and severe hypertriglyceridemia.[17,18] Patients with apo C-II deficiency may be identified by analysis of postheparin lipoprotein lipase activity (see Chapter 6), before and after the addition of exogenous apo C-II to the test assay. Genetic defects in lipoprotein lipase that lead to severe hyperchylomicronemia have included defective synthesis as well as the production of structural variants of the enzyme that are unable to hydrolyze plasma triglycerides.[17] It is important for the clinician to diagnose if the type 1 phenotype is due to a deficiency of apo C-II or of lipoprotein lipase since patients with apo C-II deficiency and acute pancreatitis can be treated with an infusion of normal plasma containing apo C-II.

C. Genetic anomalies of apo E: The genetic variation of apo E, which is the ligand for the LDL receptor–related protein (LRP; see Chapter 1A), contributes to the relatively high frequency of disturbances in the removal of chylomicron and VLDL remnants. The apo E gene is present in three common alleles termed E2, E3, and E4.[19] Apo E2—like some other very rare apo E variants[20,21]—is defective in its binding capacity to the LRP,[19] thus impairing remnant removal from the circulation. Therefore, carriers of the apo E2 allele have significantly elevated plasma remnant concentrations. However, although remnants have been shown to be atherogenic, the defective remnant catabolism does not necessarily increase the susceptibility to atherosclerosis.

In apo E2 heterozygotes (E2/E3), the mild increase in atherogenic remnants is balanced by a decrease in LDL levels, resulting in normal coronary risk. Apo E2 homozygotes (E2/E2) must be differentiated into two groups since apo E2 homozygosity is found in nearly 100% of individuals with type III hyperlipoproteinemia, but only 2% of apo E2 homozygotes develop this disease. Obviously, the development of type III hyperlipoproteinemia requires the presence of other conditions that include diabetes mellitus, kidney disease, hypothyroidism, LDL-receptor deficiency, and other forms of genetic hyperlipidemia(s).

The incidence of type III hyperlipoproteinemia is 100% only for very rare apo E variants. Furthermore, some of these apo E variants are dominant and cause type III hyperlipoproteinemia in the heterozygous state.[20] Type III hyperlipoproteinemia is characterized by elevated fasting plasma concentrations of triglycerides and cholesterol due to the accumulation of remnants and intermediate density lipoproteins (IDL). Patients have characteristic planar xanthoma and an increased risk of coronary as well as peripheral artery disease.

CLINICAL CLASSIFICATION OF PRIMARY HYPERTRIGLYCERIDEMIAS

A. Chylomicronemia (type I hyperlipoproteinemia): Fasting plasma normally does not contain chylomicrons. Lipolysis of triglyceride-rich particles can be impaired by a deficiency or synthesis of dysfunctional lipoprotein lipase or apolipoprotein C-II.[17] Homozygotes exhibit plasma triglyceride concentrations exceeding 1,000 mg/dL due to the presence of chylomicrons in fasting plasma. In both cases, lipoprotein lipase activity in postheparin plasma is extremely low. In contrast to lipoprotein lipase deficiency, in apo C-II deficiency, enzyme activity can be reconstituted by supplementing the test assay with exogenous apo C-II. Familial lipoprotein lipase deficiency is an autosomal recessive disease. Heterozygotes show a 50% reduction of lipoprotein lipase activity but normal or only slightly elevated levels of triglycerides.[17]

B. Type V hyperlipoproteinemia: In contrast to type I hyperlipoproteinemia, fasting chylomicronemia in type V hyperlipoproteinemia is accompanied by an increase in VLDL triglycerides.[22] The differentiation to type I and type V hyperlipoproteinemia can be difficult. The major differences encompass the later onset and the accompanying glucose intolerance in type V hyperlipoproteinemia.

Basic defects in type V hyperlipoproteinemia are unknown; there appear to be several defects that lead to the type V phenotype. In contrast to type I hyperlipoproteinemia, a subset of patients with type V hyperlipoproteinemia are at increased coronary risk.

C. Hepatic triglyceride lipase deficiency: Hypertriglyceridemia was also identified in two families suffering from hepatic triglyceride lipase deficiency.[23,24] The disease was also termed hyperalphatriglyceridemia because of the massive accumulation of triglycerides in HDL. The patients exhibited corneal arcus, eruptive xanthomas, palmar striae, and CHD. Unlike lipoprotein lipase, which catalyzes the hydrolysis of chylomicron and VLDL triglycerides, the preferred substrates of hepatic triglyceride lipase are triglycerides (and phospholipids) of VLDL remnants and HDL. Thus, lipoproteins of hepatic triglyceride–lipase-deficient patients are characterized by two anomalies: (1) HDL are large and consist mostly of triglycerides; (2) VLDL remnants accumulate in plasma.

The basic defect of hepatic triglyceride lipase deficiency is unknown. The disease is diagnosed by the absence of hepatic triglyceride lipase activity in postheparin plasma (see Chapter 6).

D. Remnant hyperlipidemia (type III hyperlipoproteinemia, familial dysbetalipoproteinemia, broad β-disease): As a metabolic consequence of a binding defect of apo E to the LRP, remnants of triglyceride-rich particles (i.e., chylomicrons, VLDL) accumulate in plasma.[10] Because of their behavior in ultracentrifugation and electrophoresis, these particles are termed beta-VLDL. In animals, they cause the development of severe atherosclerosis. Patients with type III hyperlipidemia suffer from tuberous xanthomas, palmar and plantar xanthomas, and peripheral and coronary artery disease. The disease is diagnosed by the presence of these clinical symptoms and by the findings of distinctly elevated levels of triglycerides and cholesterol (typically, the ratio is 1), a broad beta band upon lipoprotein electrophoresis, β-VLDL and apo E2 homozygosity, or rare apo E variants. The frequency of type III hyperlipoproteinemia in Western populations is 1/5,000.

E. Familial hypertriglyceridemia: Familial hypertriglyceridemia is diagnosed if the following criteria are given: (1) the patient has isolated hypertriglyceridemia (i.e., cholesterol <200 mg/dL, triglycerides >200 mg/dL); (2) isolated hypertriglyceridemia is also present in other family members; and (3) unlike familial combined hyperlipidemia, no family member suffers from any other dyslipoproteinemia. In contrast to chylomicronemia, restriction of dietary fat does not decrease the plasma concentration of triglycerides. The activity of lipoprotein lipase is normal or only slightly decreased. Typically, the disease is diagnosed in adults. The inheritance is autosomal dominant.

Primary hypertriglyceridemia is likely caused by the overproduction of VLDL.[14] The biochemical origin of increased hepatic VLDL production is unknown. Interestingly, the triglyceride plasma concentration correlates positively with the concentration of insulin so that insulin resistance might be relevant to the pathogenesis of the disease. Primary hypertriglyceridemia is not associated with any increased risk for pancreatitis and venous thrombosis, especially when corticosteroids or estrogens are administered to the patients.

F. Familial combined hyperlipidemia: Familial combined hyperlipidemia is a common genetic form of hyperlipidemia associated with increased risk of premature cardiovascular disease.[12] Familial combined hyperlipidemia is present in greater than 15% of CHD patients, and represents one of the most frequent genetic dyslipoproteinemias associated with an increased risk of premature cardiovascular disease. The disorder is characterized by elevated plasma cholesterol, triglycerides, or both. Individuals as well as family members of those with familial combined hyperlipidemia have multiple phenotypes. The LDL present in patients with familial combined hyperlipidemia is small and "dense" with an increased ratio of LDL apo B to cholesterol.[13,25] A subset of patients with familial combined hyperlipidemia have been identified as having hyperapobetalipoproteinemia, which is characterized by normal levels of plasma LDL cholesterol, dense LDL, and elevated plasma apo B levels.[25,26] Hyperapobetalipoproteinemia is a frequent dyslipoproteinemia observed in patients with premature cardiovascular disease and "normal lipids." The molecular defect(s) in combined hyperlipidemia is unknown. Kinetic studies have suggested that the elevated plasma apo B levels are due to increased synthesis rather than decreased catabolism.[27]

G. Hypertriglyceridemia in HDL deficiency syndromes: Hypertriglyceridemia has also been observed in patients with virtual or complete absence of lecithin:cholesterol-acyltransferase, with low HDL levels, with fish-eye disease, with apo A-I deficiencies or with Tangier disease.[28,29] However, in most affected individuals, triglycerides are only slightly increased (200–400 mg/dL), while the largely reduced HDL concentration is an easily detected hallmark. Corneal opacities are present, although to different degrees in all HDL deficiency syndromes. Other clinical syndromes are variable and include xanthomas (apo A-I deficiency), renal insufficiency, anemia (lecithin:cholesterol acyltransferase deficiency), hepatosplenomegaly, neuropathy, or abnormal tonsils (Tangier disease).

H. Familial dyslipidemic hypertension: Familial dyslipidemic hypertension is a recently described syndrome characterized by early familial hypertension (before age 60) with lipoprotein abnormalities of triglycerides, LDL and/or HDL.[30,31] Familial dyslipidemic hypertension appears to occur in 15% or more of patients with hypertension, and at least one half of patients with early familial hypertension. Kindreds with familial dyslipidemic hypertension can be divided into two subgroups. One group has familial combined hyperlipidemia with very elevated triglycerides and plasma apo B as well as insulin. The plasma lipoproteins in the other group include very low HDL and moderately elevated plasma VLDL and insulin. Small dense LDL particles as well as increased obesity were present in both subgroups of familial dyslipidemic hypertension. The identification of an association of hypertension and lipoprotein abnormalities indicates that normotensive individuals with familial combined hyperlipidemia should have annual blood pressure screening, and patients with early familial hypertension should be routinely screened for lipoprotein abnormalities.

CONCLUSION

The physician should be aware of the different genetic anomalies that can cause hypertriglyceridemia. These anomalies produce varying patterns of lipid metabolism, which have been categorized into at least eight different clinical entities of primary hypertriglyceridemia.

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4. Acquired (Secondary) Forms of Hypertriglyceridemia

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A wide range of environmental factors can influence the kinetics and the concentration of triglyceride in the circulation. These include a variety of metabolic, hormonal, and nutritional influences, as well as disease states and drugs.

Hypertriglyceridemia may be due to accumulations of chylomicrons, very-low-density or intermediate-density lipoproteins (VLDL or IDL) in the circulation. Chylomicron accumulation is generally the result of impaired lipoprotein removal, rather than excessive lipoprotein input, while accumulations of VLDL or IDL are usually the consequences of excess lipoprotein input and/or impaired removal.

In many instances, the disorders that are associated with hypertriglyceridemia are also associated with an increased cardiovascular disease (CVD) risk. Such is the case with diabetes and hypertension. In the diabetic, hypertriglyceridemia is associated both with peripheral vascular disease[1] and with coronary artery disease.[2] As mentioned in the introduction of this document, it is important that the physician be aware of underlying or concurrent disorders and take a multifactorial approach to the management of the hyperlipoproteinemia.

METABOLIC INFLUENCES

A. Diabetes mellitus: In its simplest classification, there are two diabetic disorders: insulin-dependent diabetes and non-insulin-dependent diabetes. The pathogenesis of the hypertriglyceridemia in each disorder is probably different since it will reflect the level of insulin exposed to various organs and the availability of glucose and free fatty acids, substrates for triglyceride production.[3]

In patients with uncontrolled insulin-dependent diabetes, ketosis, due to profound insulin deficiency, can be accompanied by marked hypertriglyceridemia. This is generally due to an accumulation of chylomicrons, resulting from the depressed activity of the insulin-dependent enzyme lipoprotein lipase.[4] However, it may also in part be due to changes in the chylomicron, such as the reported decrease in the ratio of apo C-II to apo C-III, that might make the chylomicron a poorer substrate for lipoprotein lipase.[5]

In certain tissues, primarily adipose tissue, lipoprotein lipase is an insulin-dependent enzyme.[6] However, insulin appears to have little effect on the enzyme in muscle.[7] Also, insulin deficiency leads to an increase in the mobilization of free fatty acids from adipose tissue. Unless there is sufficient insulin to maintain hepatic VLDL–triglyceride synthesis and secretion, however, the increased mobilization of free fatty acids does not induce an increased plasma triglyceride level.[4]

Non-insulin-dependent diabetes patients generally have higher insulin levels than insulin-dependent diabetes patients.[8] The hyperinsulinemic state of the non-insulin-dependent diabetes patient probably reflects the excess of endogenous (i.e., pancreatic) insulin secreted to compensate for an underlying insulin resistant state. Hyperinsulinemia may also develop in those diabetics treated with insulin, whether they have insulin-dependent or non-insulin-dependent diabetes. In vivo, the chronically hyperinsulinemic state leads to an increase in the production of VLDL–triglyceride.[9] Lipoprotein lipase activity may also respond poorly to insulin. The interaction of hypertriglyceridemia and hyperinsulinemia is receiving increasing attention because of the frequently concurrent existence of the two disorders[10] and because hyperinsulinemia is an independent CVD risk factor.[11] Insulin-dependent and non-insulin-dependent diabetes, especially when poorly controlled and even in the absence of gross hyperlipidemia, may be associated with changes in lipoprotein distribution and composition.[12-14] This leads to the accumulation of IDL and small low-density lipoproteins (LDL),[13,14] which are thought to be more atherogenic. Diabetes control will partially reverse these changes.[12]

B. Obesity: In the obese patient, VLDL–triglyceride production is usually increased because of accelerated production of both the lipid and apo B components.[15] The effects of obesity often relate to other coexisting metabolic abnormalities, such as insulin resistance, carbohydrate intolerance, or non-insulin-dependent diabetes mellitus and hyperinsulinemia. Hypertriglyceridemia appears to be an even greater problem in those with abdominal, in contrast to gluteo-femoral, obesity.[16] Abdominal obesity is seen more frequently in men than in women.

C. Lipoatrophy: Lipoatrophy is a rare metabolic disorder characterized by a total absence of adipose tissue. Often, this disorder affects only a specific area of the body, usually along the dermatomal distribution. However, in cases where the disorder is generalized throughout the body, there may be an accompanying hypertriglyceridemia. The basis for the hypertriglyceridemia is not clear. It may reflect a loss of adipose tissue lipoprotein lipase[17] or an increase in VLDL production.[18]

D. Hyperuricemia: Approximately 80% of patients with gout have hypertriglyceridemia, while the same percentage of hypertriglyceridemic patients have hyperuricemia. These associations may reflect a decrease in the renal excretion of uric acid or a genetic link.[19] However, because hyperlipidemia does not occur more frequently in first-degree relatives of those with gout, the association may also reflect environmental factors. These factors would include high simple sugar intake, obesity, alcohol, and certain drugs such as thiazides.

E. Glycogen storage disease (type I): This disorder is characterized by a deficiency of glucose-6-phosphatase which causes the patient to be very susceptible to hypoglycemia. When hypoglycemia occurs, the patient's adipose tissue is mobilized to supply energy needs. Free fatty acid concentrations and, subsequently, the supply of a VLDL–triglyceride substrate are increased. The condition is then compounded by an increase in glycolysis that occurs because of the glucose-6-phosphatase deficiency. The increase in glycolysis, in turn, induces an increased de novo synthesis of fatty acids and of the lipogenic intermediate malonyl CoA. Because malonyl CoA inhibits palmitoyl carnitine transferase, not only is the supply of mobilized and newly synthesized fatty acids increased, but their oxidation is reduced. Hence, the rate of fatty acid esterification increases.[20]

HORMONAL INFLUENCES

A. Insulin: The effects of insulin have already been considered in the section on diabetes. Insulin (1) increases the removal of circulating triglyceride, through its effect on lipoprotein lipase; (2) increases the supply of adipose tissue free fatty acids, one of the substrates from which the liver makes triglyceride; (3) increases de novo hepatic lipogenesis; (4) alters the balance between hepatic fatty acid oxidation and esterification; and (5) possibly, decreases apo B synthesis and lipoprotein secretion.

B. Thyroid hormones: Thyroxine and triiodothyronine can exert their effects at a variety of levels.[21] They can increase the rate of VLDL catabolism, in part, because of their effect on lipoprotein lipase and on the LDL-receptor-mediated uptake of lipoproteins. In hypothyroidism, the removal of VLDL remnants may also be impaired because of the reduction in hepatic triglyceride lipase.[22] Hypothyroidism can also directly induce an excess production of IDL, at least in patients with type III hyperlipoproteinemia.[23]

C. Sex hormones: Estrogens can reduce the activity of the plasma lipases, particularly of hepatic triglyceride lipase, and thus, impede the removal of circulating triglyceride. Estrogens can also increase the synthesis of VLDL–triglyceride and the IDL concentration and thereby induce type III hyperlipidemia in the homozygous apo E2/2 patients.[23]

Progestational hormones decrease plasma triglyceride. Testosterone and anabolic steroids have been used to treat type V hyperlipoproteinemia, perhaps because of the effect they have on hepatic triglyceride lipase.

NUTRITIONAL INFLUENCES

There are too many nutritional influences on plasma triglycerides to be able to provide more than a cursory overview. In many instances, the nutritional influences may overlap some of the factors already discussed. For example, overnutrition will result in obesity with all of its consequences.

The consumption of simple sugars, particularly fructose, can induce hypertriglyceridemia due, in part, to the insulin resistance that develops as a consequence of fructose feeding.[24] It may also be because, in the presence of dietary fructose, hyperinsulinemia exerts a greater effect on triglyceride production than is seen in the presence of glucose.[25] Finally, fructose feeding appears to alter the composition of VLDL, making it more difficult to be removed.[26]

Another nutrient that has an important impact on triglyceride levels is ethanol. Even moderate alcohol intake can result in hypertriglyceridemia in susceptible individuals. Alcohol consumption may increase the rate of lipogenesis, decrease the proportion of fatty acids that are oxidized, increase the proportion of fatty acids that are esterified, and impair triglyceride removal because of a reduction in lipoprotein lipase.[27]

DISEASE STATES

A. Metabolic disorders: (Discussed above)

B. Renal diseases: Hyperlipoproteinemia may occur with two different forms of renal disease: nephrotic syndrome and renal failure. In nephrotic syndrome, the most frequent plasma lipid abnormality is hypercholesterolemia. This reflects an increase in the plasma concentrations of LDL. The concentrations of triglyceride and of VLDL are also increased. There is no consensus with respect to high-density lipoproteins (HDL), some reporting increased, some unchanged, and some decreased levels. The composition of VLDL and of LDL does not differ from that in normal individuals.[28–30]

The causes of the lipoprotein concentration changes remain to be defined. Most agree that the production rates of both VLDL and LDL are increased.[30–32] Some feel that their catabolism is also decreased. However, that has not been a universal observation. The changes in lipoprotein turnover may result from a number of causes.[30–36] They may be a consequence of the decreased level of albumin in the serum, together with the associated changes in osmolality and/or in free fatty acid transport. They may also be associated with the loss of lipoproteins, particularly HDL, into the urine. Not only might this account for low plasma HDL levels, but it might reduce the available amounts of apo C-II, the activator of lipoprotein lipase.

The coexistence of other abnormalities such as renal failure, or glucocorticoid treatment, will also influence lipoprotein kinetics in patients with nephrotic syndrome. There is a vast body of evidence to link lipoprotein changes, such as those seen in nephrotic patients, to premature atherosclerosis in non-nephrotics. However, before reaching conclusions with respect to the role of dyslipoproteinemias as risk factors for atherosclerosis in nephrotics, the possible confounding influences of other conditions such as hypertension and clotting abnormalities must be considered.[37]

Hyperlipidemia is also seen in patients with renal failure, even in those undergoing treatment with hemodialysis or peritoneal dialysis. The most frequent abnormality is hypertriglyceridemia.[38] This reflects the accumulation of IDL. These patients may also have low HDL levels. They have an increased probability of developing premature atherosclerosis.[39] While this may result from their lipoprotein abnormalities, the impact of coexisting diseases such as hypertension and diabetes must also be recognized.

Turnover studies suggest that the hypertriglyceridemia results from a decrease in the catabolism of the triglyceride-rich lipoproteins.[40] This may be due to the presence of an inhibitor of lipoprotein lipase in the plasma of uremic patients.[41] As in the case of nephrotic patients, associated diseases and/or treatment programs may modulate the concentration and kinetics of the lipoproteins in these individuals.

C. Paraproteinemias: Hypertriglyceridemia has also been seen in paraproteinemias associated with disorders such as systemic lupus erythematosus or myeloma. These disorders are associated with inhibited triglyceride removal,[42] perhaps due to a heparin-binding protein.[43]

DRUGS

A number of drugs may induce or aggravate hypertriglyceridemia. Among these, the two most commonly encountered groups are those that are used in the treatment of hypertension and those that contain estrogens.

The antihypertensives include diuretics and β adrenergic blockers. Of the diuretics, the thiazides and chlorthalidone are the ones that are most likely to raise serum triglyceride levels. The loop diuretics (e.g., furosemide) have a less well-defined triglyceride-elevating effect, and the potassium-sparing diuretics (e.g., triamterene and spironolactone) appear to have no effect on triglycerides. In some instances, these effects on triglycerides parallel the induction or aggravation of carbohydrate intolerance. Hence, they may result from alterations in insulin–carbohydrate homeostasis. Other possible hormonal mediators of the diuretics' effects may be the catecholamines, as these may be increased during therapy with some of the diuretics.

The β-selective adrenoceptor blockers (e.g., metoprolol, atenolol, and practolol) have effects that are similar to, but less profound, than those of the nonselective blockers. Those β blockers that also have intrinsic sympathomimetic activity (acebutolol, pindolol, and oxprenolol) appear to be neutral with respect to their effects on lipoproteins. Another in this general group of drugs is labetolol. It has both β- and α-blocking effects, the former being much stronger than the latter. It also appears to be "lipoprotein neutral." One other group of adrenergic blocking drugs are the α blockers, such as prazosin. This drug also does not increase plasma triglycerides.

Two other groups of antihypertensive drugs that are increasingly being used are the calcium channel blockers (e.g., diltiazem, verapamil, and nifedipine) and the angiotensin-converting enzyme inhibitors (e.g., captopril and enalapril). These two groups of drugs do not appear to have any effect on triglycerides.

Another group of drugs that may have profound effects on plasma triglycerides are the steroids. Among these, the most frequently taken are the estrogens. The use of estrogens, either as hormonal replacement therapy or as a part of an oral contraceptive preparation, is accompanied by an increase in the levels of triglycerides in the plasma; the importance of this is greatest in those who already have underlying hypertriglyceridemia. In some of them, the estrogen-induced increase in triglycerides has been sufficient to precipitate an acute abdominal crisis. This is one of the circumstances in which the frequently observed inverse relationship between triglyceride and HDL levels in the plasma does not occur. Estrogens appear to produce their effects by increasing VLDL–triglyceride production and by decreasing the activity of hepatic lipase. Progestagens appear to oppose some of these effects of the estrogens. Thus, the overall effects of the oral contraceptives often depend on the balance between these opposite effects.

Related to this family of compounds are the androgens and the anabolic steroids. These steroids may actually result in a reduction of plasma triglycerides. The other steroid family that may alter plasma triglycerides are the glucocorticoids. They may increase plasma triglyceride concentrations both by their effects on carbohydrate-insulin homeostasis and by a direct action to increase triglyceride production.

Another group of drugs that has been used increasingly is the retinoids. These agents are particularly useful in the treatment of certain skin disorders, particularly severe acne. They may, however, produce hypertriglyceridemia as an unpredictable side effect Because of the unpredictability of hypertriglyceridemia with any of the drugs mentioned above, the plasma lipids should be monitored in patients using them. More detailed considerations of each of these drugs' effects on plasma lipoproteins are found in a series of review articles.[44–47]

CONCLUSION

Hypertriglyceridemia may be secondary to a number of metabolic, hormonal, and nutritional influences, as well as to certain disease states and drug regimens. In several cases, the metabolic or nutritional disorders that are associated with hypertriglyceridemia, including diabetes, obesity, hyperuricemia, and glycogen storage disease are also associated with an increased risk for CVD. A multifactorial approach is needed to manage properly secondary hypertriglyceridemias.

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5. Epidemiology

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During the past 30 years, numerous epidemiologic studies have addressed the question of whether elevated levels of plasma triglyceride are related to an increased coronary heart disease (CHD) risk. Despite this extensive literature, interpretation of the results have not been straightforward, and controversy still exists as to the significance of this association. The meaning of multivariate statistical results, controlling for other lipid or lipoprotein-related variables, has been difficult to determine. In particular, the metabolic interrelationships between triglyceride and high-density lipoprotein cholesterol (HDL-C) "makes it difficult indeed to evaluate the distinct risk of hypertriglyceridemia and of reduced HDL cholesterol."[1]

This section will review the epidemiologic evidence by considering results based on a variety of study designs and different populations of individuals. Case-control, angiographic and prospective studies in men, in women, and in diabetic subjects, all conducted in Western countries, will be summarized. Because cardiovascular disease (CVD) rates have traditionally been lower in Japan, studies of triglyceride and atherosclerosis in Japan will also be described.

STUDIES IN MEN

As early as 1959, the association between triglyceride and myocardial infarction (MI) was reported in a case-control study.[2] Since that time, at least 15 additional case-control or cross-sectional studies have been reported in men, generally using MI and/or angina as the endpoint of interest.[3–17]

With only one exception,[14] each of these studies found a univariate association between triglyceride and CHD. In six of these studies,[2,7,9,10,12,15] the association of triglyceride was also analyzed, controlling for either total plasma cholesterol (TC) or low-density lipoprotein cholesterol (LDL-C), and in each case the association persisted. Of the four studies in which the confounding effect of HDL-C was also considered, the triglyceride association remained significant in three,[12,15,17] and disappeared in one.[9]

In addition, many cross-sectional studies using angiographic determination of CHD severity have investigated triglyceride as a risk factor. Of 15 such studies, 12 found a univariate association between triglyceride and disease severity,[18–29] and three did not.[30–32] Of the five angiographic studies that adjusted for TC or LDL-C, the association persisted in four[23,25,26,29] and not in one.[22] Only one such study adjusted for HDL-C, and in this study the triglyceride association did not remain significant.[29]

One serious potential bias in the case-control and cross-sectional studies is that these studies cannot determine if triglyceride elevations precede the onset of CVD. This factor is particularly important since lipid levels have been shown to change after acute MI.[33] To resolve these questions, a prospective study design must be used.

In general, prospective studies in men have also shown a significant association between triglyceride and CHD, although less consistently than the case-control studies. Of 16 prospective studies, varying in follow-up from 3 to 12 years, 13 found a univariate association,[34–46] and 3 did not.[16,47,48] The results of multivariate analysis are more divergent, with the triglyceride association persisting after the adjustment for TC or LDL-C in 8 studies,[34,35,37–40,44,45] but not persisting in 4 studies.[36,41,42,46] In the 3 studies that controlled for HDL-C, none showed a significant multivariate association for triglyceride.[36,43,46]

STUDIES IN WOMEN

The studies investigating triglyceride as a risk factor for CHD in women include three early studies from Framingham, Evans County, and Rochester, Minnesota. All three studies found a univariate association between CHD and triglyceride levels.[30,42,47,49] In the Evans County study,[47] this relationship remained significant after controlling for TC, but HDL-C was not evaluated. In the Framingham Study,[42,49] triglyceride was a strong predictor among women over age 50. This result may be especially meaningful since the majority of CHD occurs among women in this age range. A series of studies in Scandinavia have consistently demonstrated a strong relationship of triglyceride with myocardial infarction, but not with angina pectoris.[40,50–52] Based on angiographic data, two studies have shown a correlation between plasma triglyceride and the severity of CHD in women.[29,32] Both demonstrated this correlation after adjusting for TC, but in only one study was the correlation independent of HDL-C.[32]

Two recent studies have considered the association of triglyceride and CHD mortality in women. In the Lipid Research Clinics Follow-up study of 8.5 years, only a borderline association was reported ($p=0.089$), although the relative risk was 2.2.[43] This association decreased somewhat with the adjustment for LDL-C and HDL-C as well. In an ecologic study of CHD mortality rates in 19 countries, however, no association was found.[14]

STUDIES IN DIABETICS

It is well established that the risk for CHD is increased in diabetics and that risk factor levels are also elevated.[53,54] Four recent studies, two cross-sectional and two prospective studies, have considered the role of plasma triglycerides in the risk of CHD among diabetics.

In a substudy of the WHO multinational study, the association of serum triglyceride levels and ischemic heart disease was considered among 1,911 "established diabetic patients" in the age range of 35 to 54 years from five sites.[55] In these cross-sectional data, triglyceride levels were significantly higher among subjects with major Q-wave abnormalities compared with subjects without such abnormalities. Multivariate analysis using logistic regression revealed that the triglyceride association remained significant and independent of age, adiposity, cholesterol, and systolic blood pressure. However, HDL-C was not considered in the analysis.

In a cross-sectional study of 1,059 Finnish subjects with non-insulin-dependent diabetes, ages 45 to 64 years, triglyceride was significantly associated with definite MI in both men and women.[56] In a separate publication, multivariate analyses in the same sample of diabetic subjects were reported, including TC and HDL-C as covariates.[57] In these models, triglyceride was not independently associated with definite MI, probable CHD, or angina pectoris in men or women.

In the Schwabing study, 520 diabetic outpatients, ages 17–84, were followed for 5 years for incidence of major vascular events (including cardiovascular death, stroke, significant coronary heart disease, and gangrene).[58] Subjects with a major vascular event had higher age-adjusted mean triglyceride levels, although the result was only of borderline significance in men. The results in women remained significant in multivariate analyses including systolic blood pressure, duration of diabetes, and several interaction terms. Multivariate analyses including other lipid measurements were not reported.

In the Paris Prospective Study, men ages 43–54 years with either impaired glucose tolerance or diabetes were followed for an average of 11 years.[55] Baseline triglyceride levels were significantly higher in men with death caused by CHD, and this association persisted after the adjustment for a number of other risk factors including smoking, systolic blood pressure, body mass index, and cholesterol.

STUDIES IN JAPAN

Traditionally, the incidence of CHD has been substantially lower in Japan than in the industrialized West. It has been generally thought that this is, in part, related to the lower serum lipid levels among the Japanese individuals when compared with Western subjects. Over the past few decades, however, the incidence of CHD in Japan has been increasing. This change appears to parallel the westernization of diet and the gradual increase in the lipid levels seen in Japan since World War II.[60,61]

A. Trends in serum lipid levels in Japan: Since the 1960s, the serum lipid levels of the Japanese population have been monitored in a large, multicenter trial.[62,63] Analysis of the data clearly shows an increase in both serum TC and triglyceride levels. From 1960 to 1980, mean serum TC levels increased by 15 mg/dL, and from 1970 to 1980, triglyceride levels in subjects older than age 50 increased by more than 10 mg/dL. The 1990 survey data show additional increases in both TC and triglyceride levels. This trend is in contrast to data from the United States showing that the national effort to lower serum cholesterol levels is bringing positive results. In comparing the 1980s Japanese TC and triglyceride levels with the Lipid Research Clinics 1979 data,[64] it is evident that both serum TC and triglyceride levels are higher in Japanese than in American individuals under 30.

B. Trends in serum triglycerides and atherosclerotic disease: In the past 10 years, many investigators in Japan have explored the association between serum triglyceride levels and atherosclerotic CHD. In a cross-sectional study among hyperlipidemic patients in Japan,[65] the association of triglyceride with the prevalence of CHD was significant in familial hypercholesterolemic patients even after correction for serum TC levels. Of the case-control studies with myocardial infarction or angina pectoris as the endpoint, two showed a univariate association between triglycerides and CHD,[66,67] while in the other two studies,[68,69] serum triglyceride levels were not significantly higher in patients with atherosclerotic coronary disease than in normal controls. Of the three case-control studies considering cerebrovascular diseases as the outcome, two[70,71] showed significantly higher serum triglyceride levels in patients suffering from cerebral infarction than in normal controls, while no association was seen in patients with cerebral bleeding.[72]

CONCLUSION

Although the literature on epidemiologic associations between plasma triglyceride and CHD is not completely consistent, important trends do emerge. The majority of studies demonstrate a significant univariate relation, although the results of case-control and cross-sectional studies are more uniform than those from prospective study designs. In many, but not all studies, triglyceride remains a significant predictor of CHD in multivariate statistical analyses controlling for TC or LDL-C. Perhaps the least consistent result is that the triglyceride association does not persist in some analyses controlling for HDL-C, while in other studies the association remains significant. Although most studies have been conducted in men, the studies providing data on women and diabetic subjects have generally found triglyceride to be a risk factor. In Japan, where the gradual rise in serum lipid levels has been associated with increased incidence of CHD, the role of triglyceride in atherosclerotic cardiovascular disease deserves additional study.

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6. Laboratory Procedures

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Triglycerides are transported to a major extent in the chylomicron as well as in the very-low-density lipoprotein (VLDL) fraction of human plasma (Table II). Triglyceride makes up approximately 90% of the chylomicron mass and 50% of the VLDL mass. In dyslipidemia, appreciable amounts of triglyceride may be transported in addition in intermediate-density lipoprotein (IDL)/β-VLDL. The triglyceride content of these fractions varies from 15 to 30%. All other lipoproteins—low-density lipoprotein (LDL), lipoprotein (a) [Lp(a)], and high-density lipoprotein (HDL)—contain triglyceride equal to 3–6% by mass.

While plasma cholesterol values are rather stable and acutely not very much influenced by diet, the fluctuations of triglycerides following meals are rather striking and vary to a great extent from person to person. Since humans normally are only a few hours in the "fasting state" during any 24-hour period, postprandial measurements of triglycerides may reflect the atherosclerotic risk of a given individual more appropriately than fasting triglyceride values (see Chapter 2). However, triglycerides are usually measured in 12- to 14-hour fasting samples.

Plasma triglyceride concentrations are profoundly influenced by the lipase activities as well as other enzymes involved in the overall lipoprotein metabolism, e.g., lecithin:cholesterol acyltransferase and cholesteryl ester transfer protein. In order to assess the underlying defect of a given hypertriglyceridemia, the presence of apo C-II mutants, of apo E isoforms, and the levels of HDL and LDL must be assessed.

It is also worth noting that chylomicron—and possibly also VLDL remnants—may be the most atherogenic triglyceride-containing lipoproteins. This chapter, therefore, will concentrate on the methodology characterizing the type of hypertriglyceridemia in a specialized laboratory, giving emphasis to those methods that prove to be most practical and precise. Since a global picture cannot be given here, the reader is referred to special literature.[1–3]

ANALYSIS OF TRIGLYCERIDES IN PLASMA (SERUM)

A. Wet chemistry methods: It seems to be generally agreed that enzymatic procedures are the methods of choice in the clinical routine laboratory. Nonenzymatic tests based on several different chemical reactions (Hantsch reaction, chromotropic acid method) are no longer in use.[4] Such enzymatic kits are available from many companies, e.g., Bio-Merrieux, Biotrol, Boehringer Mannheim, Merck, Wako, and others. Although we found differences with respect to linearity and accuracy of assays from various companies, especially if triglycerides were measured in lipoprotein fractions, no preference for a particular test is given here. For more sophisticated measurements of triglycerides in samples other than plasma, it might be advisable to evaluate the accuracy and linearity of individual tests beforehand.

There are several enzymatic triglycerides assays on the market, the most common ones being: (1) the color tests, (2) the UV tests, and (3) the test combination that does not recognize free glycerol. Tests 1 and 2 are based on a first reaction of lipases that hydrolyze glycerides quantitatively giving yield to free glycerol. Test 3 destroys in a first reaction any resident free glycerol followed by the lipase reaction in a second step. If tests 1 and 2 are used, 10 mg/dL (0.11 mmol/L) or 7% of the total triglyceride may be subtracted from the measured triglyceride values as a rough average bias. There are, however, conditions (diabetes mellitus, kidney diseases, etc.) in which free glycerol values are significantly elevated,[5] and test 3, which accounts for the free glycerol in the sample, becomes the method of choice.

The color tests are based on various chemical reactions, the GPO-PAP method being the most common. In the UV test, the conversion of NADH to NAD^+ are the final pair of substances that are followed in UV light. UV and color tests give comparable results and correlate very well.[6] Thus, many autoanalyzers are set up with the color test since it is easier to handle.

SAMPLE PREPARATION: Triglycerides may be measured in plasma or serum. To measure triglycerides

TABLE II Human Plasma Lipoproteins Ranked According to TG Content

Lipoprotein	Density (kg/L)	Mass (kDa)	% of Lipoprotein Mass				
			Protein	TG	PL	FC	CE
Chylomicrons	<1.000	<150	2	90	5	1	2
VLDL	<1.005	5–130	10	54	16	7	13
IDL	<1.019	3.5	17	20	20	9	34
HDL$_2$	<1.125	0.36	42	6	34	5	13
LDL	<1.063	2.5	23	4	21	11	41
Lp(a)	<1.100	5.5	34	3	18	9	36
HDL$_3$	<1.21	0.2	56	3	23	3	15

PL = phospholipid; FC = free cholesterol; CE = cholesteryl esters; TG = triglyceride

in plasma by the GPO-PAP method, heparin or EDTA must be used as an anticoagulant. Serum/plasma samples may not be stored for more than 2–3 hours at room temperature. At 4°C, samples are stable up to 4 days, at –20°C, at least 1 month.

B. Dry chemistry methods: Dry chemistry on solid phase have gained wide acceptance in routine analysis of triglycerides.[7] These methods, using different enzymatic test principles, are offered by various companies, e.g., Ames (Seralyzer), Boehringer Mannheim (Reflotron), Kodak (Ektachem DT 60), Kyoto Daiichi (Spotchem), and Roche (Cobas Ready).

SAMPLE PREPARATION: As in wet chemistry, the dry chemistry methods for triglycerides use serum or plasma samples. A few systems (e.g., Reflotron) additionally allow the determination of triglycerides directly in whole blood (capillary or venous). This procedure, providing test results within 3 minutes, facilitates on-the-spot diagnosis.

TRIGLYCERIDE ASSAYS IN LIPOPROTEIN FRACTIONS

A. Precipitating agents: Most of the precipitating agents for assaying HDL cholesterol are equally suited to measure triglyceride contents. Since there is a great number of such reagents on the market, physicians should ask whether such reagents are compatible with the appropriate triglyceride assays. Special attention is necessary if polyethylene glycol is used as a reagent, since many batches give very high backgrounds because of the appreciable amounts of free glycols.

B. Ultracentrifugation[8]:

VLDL–TG: To measure triglycerides in VLDL, plasma or serum samples are overlayered with 0.15 mol/L NaCl solutions (isotonic saline) and centrifuged for 18 hours at 120,000×*g* in a fixed angle or swinging bucket rotor. Care must be taken to cut the tubes at the appropriate position or aspirate the top layer by a syringe. Triglycerides are normally measured in the bottom fraction and VLDL–triglycerides are calculated by subtraction from total plasma triglycerides.

IDL–TG: The bottom fraction obtained after VLDL removal is adjusted to a density of approximately 1.040 and overlayered with NaCl of density 1.019. All further steps are equal to those for VLDL separation. Under these conditions, IDL float to the top and may be assayed for triglycerides. Beside the stepwise procedures, there are numerous publications describing single-step isolation of triglyceride-rich lipoproteins in density gradients, using swinging bucket or zonal rotors.[9–11] It must be mentioned here that high salt concentrations interfere to a variable degree with various triglyceride assays. Interference also occurs if samples are dialyzed, as most dialysis bags are stabilized with glycerol.

ANALYSIS OF PARAMETERS INFLUENCING PLASMA TG VALUES (TABLE III)

A. Postheparin lipolytic activity: After intravenous administration of heparin, mainly two types of lipases, lipoprotein lipase and hepatic triglyceride lipase, are released into the plasma. These lipases must be determined individually in order to characterize the basic defect of any hypertriglyceridemia.

TABLE III Laboratory Parameters Relevant for Typing Hypertriglyceridemias

Parameter	Method	Reference
PHLA (LPL, HL)	Radioassay	12,14
	Antibody	13
LCAT	Radioassay	15,16
CETP	Radioassay	17
VLDL-TG, IDL-TG	Ultracentrifuge	8–11
LDL-C	Friedewald formula	20
	Ultracentrifuge	8
HDL-C	Precipitation	18
HDL$_2$-C	Precipitation	19
Apolipoproteins	Immunoassays	21
Apo E isoforms	Isoelectric focusing	22,23
Apo C-II	Western blotting	24
Apo B variants	Molecular biology	25

LPL = lipoprotein lipase; HL = hepatic lipase; LCAT = lecithin:cholesterol acyltransferase; CETP = cholesteryl ester transfer protein; PHLA = postheparin lipolytic activity

Although most of the methods proposed sound rather straightforward, the postheparin–lipolytic activity assay is probably one of the most complicated methods of the lipoprotein laboratory. This relates not only to the different kinetics of both lipases, but also to the heterogeneity of the substrate (postheparin–lipolytic activity hydrolyzes both triglycerides and phospholipids).

For the release of postheparin lipolytic activity from endothelial surface, 100 units of heparin per kg of body weight are injected intravenously, and citrate plasma samples are drawn 10, 20, and 30 minutes thereafter.

The most commonly used method to assay the enzymes is that of Krauss et al.[12] or any modification of it, using radiolabeled triglyceride emulsions. In a first step, total activity is measured followed by a second assay performed after inactivation of lipoprotein lipase by protamine sulfate. As protamine sulfate binds to many serum proteins, the actual amount necessary for lipoprotein lipase inactivation may vary significantly from sample to sample Thus, whenever possible, a specific antibody that either removes lipoprotein or hepatic lipase should be used instead.[13] Another possibility might be to use substrates that can be hydrolyzed selectively only by one type of lipase.[14]

B. Lecithin:cholesterol acyltransferase: Lecithin:cholesterol acyltransferase is another important enzyme in this context. There are two basic activity assays known: the Stokke-Norum and the Glomset and Wright methods.[15] While the former uses endogenous substrate only, the latter is based on the saturation of the incubation mixture with exogenous HDL. Thus, the activities obtained may differ quite substantially. In addition to the measurement of activities, lecithin:cholesterol acyltransferase mass is now assayed immunochemically by ELISA and RIA using polyclonal or monoclonal antibodies. Lecithin:cholesterol acyltransferase deficiencies may be caused by structural defects of the enzyme. In such cases, lecithin:cholesterol acyltransferase mass may be normal, but its activity reduced.

We have modified and combined some earlier lecithin:cholesterol acyltransferase assays yielding a procedure that can be performed on a relatively large scale and short period of time.[16] The lecithin: cholesterol acyltransferase activity may be expressed in rate units (percentage per hour) or in transfer activity (nmoles FC/mL/h).

C. Cholesteryl ester transfer protein: Cholesteryl ester transfer protein transfers/exchanges core lipids from/between lipoproteins of higher density ($HDL_{2/3}$) to those of lower density (VLDL/IDL/LDL). Here again, the measured activity depends on the presence of various amounts of endogenous substrate. A method that is independent of that has been recently proposed.[17] Similar to lecithin:cholesterol acyltransferase, cholesteryl ester transfer protein mass may be measured immunochemically.

DETERMINATION OF HDL AND LDL CHOLESTEROL

A. HDL cholesterol (HDL-C): There are many commercial kits on the market using a large array of agents, such as phosphotungstic acid, heparin/Mn^{2+}, dextran sulfate/Ca^{2+}, and many others, to precipitate selectively the apo B–containing lipoproteins [VLDL/IDL/LDL + Lp(a)].[18] In the supernatant, cholesterol, triglycerides, or phospholipids may be assayed enzymatically. In addition, HDL_2 and HDL_3 may be assayed individually by the use of precipitating agents. In that respect, polyethylene glycol in our hands gives results that correlate most favorably with those obtained by preparative ultracentrifugation.[19]

Preparative and analytical ultracentrifugation still remain the reference methods for the quantization of individual lipoprotein density fractions.[8] These methods, however, cannot be applied on a large scale and hardly account for the contamination of HDL by apo B–containing lipoproteins [Lp(a) and others].

B. LDL cholesterol (LDL-C): LDL-C is mostly calculated by the Friedewald formula[20]:

$$\text{LDL-C} = \text{TC} - \text{HDL-C} - \text{TG}/5$$

The Friedewald formula proved to be rather precise for samples with triglyceride values <400 mg/dL. Above this, it should be preferable to measure LDL-C directly.[8]

APOLIPOPROTEIN ASSAYS

A. Apolipoprotein levels: Apolipoproteins trigger the whole lipoprotein metabolism, including triglycerides, and thus may be assayed quantitatively by the use of any immunochemical method. The most frequently quantified apolipoproteins are apo B, apo A-I/A-II, and Lp(a).[21]

Of more urgent interest than the amount of a given apolipoprotein is the question of whether genetic polymorphic forms or mutants may be causing hypertriglyceridemia. Here the apo E and C-II are the most prominent ones.

B. Apo-E isoforms: Apo E exists in various isoforms differing mostly by charge differences of the protein. The most common forms are E2, E3 (wild type), and E4. Isoforms are more easily separated by isoelectric focusing of plasma in a pH gradient of 4–6, followed by Western blot analysis. There are a great number of assays described in the literature. Two of them are particularly effective.[22,23]

C. Apo C-II: Its absence in the plasma or the presence of inactive genetic variants of apo C-II are accompanied by hypertriglyceridemia resembling type I hyperlipidemia. Apo C-II may be assayed using isoelectric focusing, followed by Western blotting,[24] or by any quantitative immunochemical assay.

Molecular biology methods are becoming more applicable on a routine basis[25] as, for example, restriction fragment length polymorphism (RFLP), polymerase chain reaction (PCR), and others. These new methods in the near future will open up a completely new way of classifying hyperlipoproteinemias and dyslipoproteinemias.

CONCLUSION

Any differential diagnosis of hypertriglyceridemia has to include the measurement of HDL-C and LDL-C. In special cases, apolipoprotein concentrations as well as isoform patterns may be analyzed. In addition, the assessment of enzyme activities, such as postheparin lipolytic activity, lecithin:cholesterol acyltransferase, and cholesteryl ester transfer protein, is useful in defining the underlying defect in hypertriglyceridemia.

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7. Management of Hypertriglyceridemic Patients

A. TREATMENT CLASSIFICATIONS AND GOALS

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Two European conferences were held in 1986 and 1987 to discuss the primary prevention of coronary heart disease (CHD) and the recognition and treatment of hyperlipidemia in adults. Meanwhile, expert panels in the United States developed documents on the treatment of hypertriglyceridemia and hypercholesterolemia, although the document on hypertriglyceridemia may not be consistent with current opinion.[1] These various statements recognize that in addition to dyslipidemia, several other cardiovascular disease (CVD) risk factors are important (hypertension, cigarette smoking, sex, family history, diabetes mellitus, low high-density lipoprotein [HDL] cholesterol, and obesity).

The European guidelines and the U.S. guidelines have many points in common but differ in several important emphases. The 1984 NIH Consensus Conference on Hypertriglyceridemia in the United States defined hypertriglyceridemia as a fasting value greater than 500 mg/dL, with 250–500 mg/dL given as borderline.[1] The most recent guidelines of the National Cholesterol Education Program in the United States lists triglycerides greater than 1,000 mg/dL as a risk factor for abdominal pain and pancreatitis.[2] The triglyceride concentration enters the calculation for low-density lipoprotein (LDL) cholesterol but otherwise does not play a part in the algorithm for diagnosis and management of hypercholesterolemia.

In contrast, the European guidelines for the treatment of dyslipidemias use a combination of the total cholesterol, triglyceride, other risk factors, and the presence or absence of coronary disease in its algorithm.[3,4]

ISOLATED MODERATE HYPERTRIGLYCERIDEMIA

Patients with plasma cholesterol values below 200 mg/dL (5.2 mmol/L) and triglyceride levels between 200 mg/dL (2.3 mmol/L) and 400 mg/dL (4.5 mmol/L) are defined as having isolated moderate hypertriglyceridemia (Table IV). The underlying cause of the hypertriglyceridemia should be determined. The hypertriglyceridemia may be caused genetically, as in the case of familial hypertriglyceridemia and familial combined hyperlipidemia. Secondary causes may include obesity, excessive alcohol consumption, diabetes, estrogen therapy, renal failure, and antihypertensive agents, in particular β-blockers or thiazide diuretics. Secondary hypertriglyceridemia should be treated by treating the underlying cause.

Of considerable current interest is the clustering of hypertriglyceridemia with low HDL concentrations, hypertension, obesity, and insulin resistance. This syndrome has been termed "syndrome X" by Reaven and others.[5]

If the patient is overweight, calories should be reduced, and the primary focus should be on weight. In the basic diet, daily fat consumption should be restricted to no more than 30% of the total caloric intake, with an approximate equal distribution between monounsaturated, polyunsaturated, and saturated fat.[4,6] Cholesterol intake should be less than 300 mg per day. Both cholesterol and triglyceride levels should be monitored. (Additional dietary suggestions are reviewed in Chapter 7B.) It is not clear whether these individuals are susceptible to a high consumption of sugars or simple carbohydrates. Restriction of these carbohydrates may be required in some individuals. If needed, a fibric acid derivative or nicotinic acid would be the drug of choice, but the great majority of the patients with mild hypertriglyceridemia can be managed with dietary control alone.

While treatment of isolated moderate hypertrigylyceridemia may be controversial, there is ample evidence that triglyceride-rich remnant lipoproteins are atherogenic and that hypertriglyceridemia frequently occurs in patients with coronary disease, particularly in association with low levels

TABLE IV Management Suggestions for Hypertriglyceridemia

Isolated Moderate Hypertriglyceridemia (HTG)	Consider Contributing Causes	With Persistent HTG and One of the Following	Treat with
Triglycerides 200–400 mg/dL[*] (2.3–4.5 mmol/L) Total cholesterol < 200 mg/dL (<5.2 mmol/L)	Genetics Diabetes Obesity Renal failure Alcohol excess Estrogen therapy Beta blockers; thiazides	Personal history of CVD[†] Family history of CVD Familial combined hyperlipidemia Familial dysbetalipoproteinemia Familial HTG Diabetes HDL cholesterol <35 mg/dL LDL cholesterol >130 mg/dL Smoking Hypertension Male Sex	Diet[‡] Drugs[§]
Mixed HTG	**Consider Contributing Causes**	**With Persistent HTG and LDL cholesterol >130 mg/dL**	**Treat with**
Triglycerides 200–400 mg/dL (2.3–4.5 mmol/L) LDL cholesterol >130 mg/dL (>3.4 mmol/L)	Genetics Type III hyperlipidemia Familial hypercholesterolemia Diabetes Obesity Renal failure Nephrosis Hypertension Alcohol excess Estrogen therapy Beta blockers; thiazides		Follow NCEP[‖] or European Guidelines (Group D)[¶]
Severe HTG	**Consider Contributing Causes**	**With Persistent HTG**	**Treat with**
Triglycerides >400 mg/dL (>4.5 mmol/L)	Genetics Familial HTG Familial lipoprotein lipase deficiency Familial apo C-II deficiency Type III hyperlipidemia Type V hyperlipidemia Diabetes Obesity Renal failure Nephrosis Hypertension Hypothyroidism Alcohol excess Estrogen therapy Beta blockers; thiazides		Diet Drugs[§]

[*] TG ≥400 mg/dL cutoff point has been selected due to the technical limitation in estimating LDL cholesterol (see Chapter 6).

[†] More aggressive treatment may be considered.

[‡] According to recommendations of the American Heart Association and the European Guidelines.

[§] If diet alone fails and the patient remains at high risk for CVD or pancreatitis (TG > 1,000 mg/dL), drug treatment may be considered. Use of a drug to reduce CHD risk in such patients is controversial and its efficacy on CHD has not been established.

[‖] See reference 2.

[¶] See references 3 and 4.

of HDL. Treatment of moderate hypertriglyceridemia should be considered in the presence of known coronary disease, familial combined hyperlipidemia, type III hyperlipidemia, familial hypertriglyceridemia with a family history of CHD, renal diseases, diabetes mellitus, HDL cholesterol under 35 mg/dL or LDL cholesterol over 130 mg/dL, smoking, and hypertension. In general, males are at higher risk than females. In addition, elevated serum LP(a) and serum fibrinogen concentrations are recognized as coronary risk factors; their presence may put the hypertriglyceridemic individuals at higher relative risk.

MIXED HYPERLIPIDEMIA

Patients with an LDL cholesterol level >130 mg/dL (3.4 mmol/L) and a triglyceride level of 200–400 mg/dL (2.3–4.5 mmol/L) are defined as having mixed hyperlipidemia (Table IV). In treating these patients, the overall risk of CHD should be assessed, and the underlying cause of the hypertriglyceridemia should be determined and treated. The diagnostic possibilities are the same as those described above for isolated moderate hypertriglyceridemia, except that these patients might also have familial dysbetalipoproteinemia, familial hypercholesterolemia, nephrosis, or hypothyroidism.

Although the lipid elevations are often mild, mixed hyperlipidemia carries an increased CVD risk. Patients, especially those with non-insulin-dependent diabetes mellitus (NIDDM), often have depressed HDL levels as well. These patients may also have abdominal, or male-type, obesity, relative insulin resistance, and hyperinsulinemia. Hypertension has also been described in association with this syndrome. Moreover, the LDL and HDL particles are small, dense, and have an increased content of apo B-100. The term "hyperapobetalipoproteinemia" has been used to describe this condition.

These lipids/lipoprotein anomalies probably contribute to the enhanced risk of CHD and peripheral vascular disease in NIDDM patients. Indeed, the recent European Consensus on NIDDM stated: "In view of the importance of cholesterol and triglyceride as risk factors for macrovascular disease in NIDDM, it is strongly recommended that total cholesterol, HDL cholesterol and triglyceride are checked annually. If results are abnormal and intervention is appropriate, values should be checked every 3 months."[7]

In patients with mixed hyperlipidemia, every effort should be made to exclude potential secondary causes. For example, in a diabetic patient, in order to determine whether hyperlipidemia is primary or secondary, it is first necessary to bring the diabetes under good control. If the patient then remains hyperlipidemic, the hyperlipidemia is said to be primary. If the hyperlipidemia is corrected by the control of the diabetes, the hyperlipidemia is said to be secondary.

Mixed hyperlipidemia is greatly exacerbated by obesity. If the patient is overweight, a calorie-restricted diet[3,6] should be prescribed. Every effort should be made to control the hyperlipidemia with diet or a combination of diet and exercise before using drugs. However, drug treatment should be considered if the overall risk of CHD is high, particularly if LDL cholesterol or triglyceride levels remain high, or HDL cholesterol levels remain low. At the present time, the fibric acid derivatives appear to be the drugs of choice if glucose intolerance is present. A recent report also indicates an effective use of HMG-CoA reductase inhibitors in NIDDM patients with mixed hyperlipidemia. Nicotinic acid is very useful but will often exacerbate diabetes.

As yet, there have not been any primary prevention trials specifically testing the effects of triglyceride-lowering therapy on CHD risk. Nonetheless, subgroup analyses of data from several cholesterol studies have demonstrated the combined benefits of cholesterol and triglyceride modification.

In the Helsinki Heart Study, patients with mixed hyperlipidemia (type IIb) who took the fibric acid derivative gemfibrozil showed the largest reduction in coronary events.[8] Furthermore, in two secondary prevention trials, patients treated with nicotinic acid, a drug with potent hypotriglyceridemic effect, had fewer coronary events and less overall mortality than did controls.[9,10] In one of these secondary trials, namely the Stockholm Ischemic Heart Disease Study, the reduction in mortality was greater the more the triglycerides were lowered.[9] Finally, patients in two angiographic studies, in which nicotinic acid and bile acid resin were used as part of the lipid-lowering therapy, experienced atherosclerotic regression.

The results so far reported from the Cholesterol Lowering Atherosclerosis Study (CLAS)[11,12] and the Familial Arteriosclerosis Treatment Study (FATS)[13] show a stabilization and/or regression of coronary plaques in patients vigorously treated with drugs that decrease LDL and triglycerides while raising HDL cholesterol. However, the isolated effect of raising HDL remains to be established. Two other studies using coronary arteriography, the Leiden Diet Trial[14] and the NIH Type II Coronary Intervention Trial,[15] showed that the best predictor of atherosclerosis progression was the ratio of total to HDL cholesterol. There have been no clinical trials in which hypertriglyceridemic patients were specifically recruited; the trials mentioned above are suggestive, but not definitive. Therefore, the use of drugs for triglyceride lowering is done with incomplete information and should be based on clinical judgment.

SEVERE HYPERTRIGLYCERIDEMIA

Patients with triglyceride levels >400 mg/dL (4.5 mmol/L) are defined as having severe hypertriglyceridemia (Table IV). Patients in this group should be cared for by specialists in lipid metabolism, who should attempt to provide a precise diagnosis of the underlying metabolic defect and initiate treatment. Possible underlying causes of severe hypertriglyceridemia must be excluded and treated. In addition to the probable causes discussed above, the specialist must also rule out familial hypertriglyceridemia, familial type V hyperlipidemia and chylomicronemia syndrome, either due to familial lipoprotein lipase deficiency or familial apo C-II deficiency. Potential secondary causes include uncontrolled diabetes mellitus, hypothyroidism, and glycogen storage disease.

The initial treatment approach for these patients is a diet recommended for moderate hypertriglyceridemia.[4,6] Also, alcohol consumption should be totally eliminated, and the patient should be placed on a weight-reducing diet if he or she is obese. If fat intake is severely restricted, then dietary long-chained fatty acids may be supplemented by medium-chained triglyceride. A fat-modified lipid-lowering diet should also emphasize the consumption of omega-3 fatty acids and cold water fish, including salmon, mackerel, sardines, tuna, and herring.

If the underlying cause of the severe hypertriglyceridemia is familial lipoprotein lipase deficiency or familial apo C-II deficiency, then drug therapy is not useful. However, drugs can be used successfully to treat familial hypertriglyceridemia and all other forms of severe hypertriglyceridemia. Fibric acid derivatives are the drugs of choice. Nicotinic acid is also extremely effective, but it must be used with great caution if the patient is diabetic.

HYPERTRIGLYCERIDEMIA AND LOW HDL LEVELS

As discussed in the earlier sections, triglyceride elevations are closely associated with low HDL concentrations. In the Helsinki Heart Study, the combined effect of lowering LDL and raising HDL caused a 34% reduction in CHD events over a 5-year period, as compared with a double-blinded placebo group.[8] The fibric acid derivative gemfibrozil was used in this study. A marked reduction in triglycerides also occurred, but the statistical analysis failed to indicate triglyceride as an independent CHD predictor. Recent reviews by Austin and others have shown the inappropriateness of the current statistical methods of looking at triglyceride as an independent risk factor, since it is so closely tied to the HDL cholesterol level.[16] On the basis of the Helsinki results, the FDA in the United States expanded the indication of gemfibrozil for the prevention of CHD in type IIb patients (with elevated triglycerides and depressed HDL), if dietary and first-line drug therapy are ineffective.

A recent analysis of the Prospective Cardiovascular Munster (PROCAM) Study strongly supports the concept that the combined effects of hypertriglyceridemia (>200 mg/dL, 2.3 mmol/L) and low HDL cholesterol (<35 mg/dL, 0.9 mmol/L) in individuals affected by elevated ratios of total to HDL cholesterol (>5) is associated with a high risk of CHD (Figure 2).[17] The definition of "high-risk individuals" according to this epidemiologic data requires the simultaneous determination of total cholesterol, triglyceride, and HDL-cholesterol.

Extensive data analysis of several epidemiologic and intervention studies by Gordon et al. also strongly supports the involvement of HDL in CHD.[18] In the Coronary Primary Prevention Trial (CPPT), the patients with HDL cholesterol levels <33 mg/dL, did not experience a rise in their HDL levels during the trial nor a reduction in CHD events, even though their LDL levels were reduced.

Based on the results of these various clinical trials and epidemiologic studies, depressed HDL levels in hypertriglyceridemic patients appear to increase the risk of atherosclerosis and, by implication, the need for treatment. Low HDL levels often are associated with a lack of exercise, cigarette smoking and obesity. Antihypertensive treatment with β-blockers or diuretics may also lower HDL concentrations.

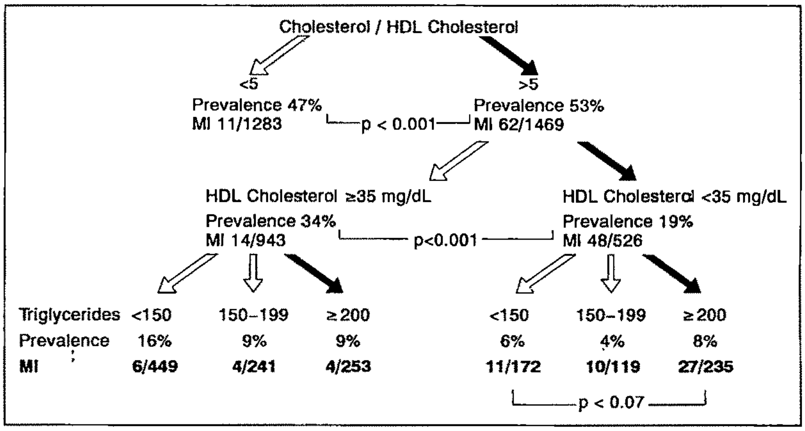
Cholesterol / HDL Cholesterol
<5
>5
Prevalence 47%
MI 11/1283
p < 0.001
Prevalence 53%
MI 62/1469
HDL Cholesterol ≥35 mg/dL
Prevalence 34%
MI 14/943
p<0.001
HDL Cholesterol <35 mg/dL
Prevalence 19%
MI 48/526
Triglycerides <150 150–199 ≥200 <150 150–199 ≥200
Prevalence 16% 9% 9% 6% 4% 8%
MI 6/449 4/241 4/253 11/172 10/119 27/235
p < 0.07

FIGURE 2. PROCAM Study: dyslipidemia and risk of CHD. Prevalence of dyslipidemia and myocardial infarction (MI) in the Prospective Cardiovascular Munster (PROCAM) Study.[17]

CONCLUSION

Triglyceride levels should always be analyzed after an overnight fast, and at least two or three measurements should be made prior to the diagnosis and determination of treatment. Secondary causes of hypertriglyceridemia should be identified and treated appropriately. The treatment of moderate hypertriglyceridemia (200–400 mg/dL) is warranted in the presence of familial combined hyperlipidemia, familial dysbetalipoproteinemia, existing coronary artery disease, a family history of coronary heart disease, diabetes mellitus, chronic renal disease, low levels of HDL cholesterol, or elevated LDL cholesterol.

Many hypertriglyceridemic patients can reduce their triglyceride levels through dietary and other nonpharmacologic approaches, such as weight reduction and appropriate exercise. If nonpharmacologic treatment proves ineffective, drug therapy may be considered, although this remains controversial. Fibric acid derivatives, nicotinic acid, and nicotinic acid derivatives are the drugs of choice.

Patients with very severe hypertriglyceridemia (>1,000 mg/dL or 11.2 mmol/L) are at risk of pancreatitis. In this group, more rigorous dietary fat restriction (<20% total calories) is required.

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B. DIETARY MANAGEMENT OF HYPERTRIGLYCERIDEMIC PATIENTS

R. Carmena, MD, and S .M. Grundy, MD (Reviewer)

Dietary therapy should always be the first approach to treating hypertriglyceridemia. Dietary factors (caloric content, type of fat, and carbohydrate and alcohol intake) influence serum triglyceride levels through several mechanisms.[1,2]

Hypercaloric diets have been shown to stimulate the formation of triglycerides in the liver, promoting the secretion of VLDL particles. In addition, obesity frequently causes secondary hypertriglyceridemia, a condition usually corrected by reducing the caloric intake. Thus, a primary objective of dietary treatment for hypertriglyceridemia is an adequate supply of daily calories in order to achieve and/or maintain the ideal body weight. Regular aerobic physical exercise may be useful both in reducing body weight and in correcting hyperinsulinemia, which is frequently associated with hypertriglyceridemia.[3-4]

Amounts and types of fats are important in the dietary treatment of hypertriglyceridemia. In familial lipoprotein lipase and apo C-II deficiency (type I), hypertriglyceridemia is aggravated by dietary fat and is best treated by stringent reduction (less than 15–20% of daily energy) of fat intake to reduce chylomicron input. An optimal fat intake should be identified for each type I patient, and for most, the diet must be a restricted one.[5] Medium chain triglycerides, which are absorbed by the portal vein and do not generate chylomicrons, can be used in cooking or as salad dressing as a supplement to normal dietary long-chain fatty acids once the optimal fat intake has been identified. A transient increase in very-low-density lipoprotein (VLDL) triglyceride may be induced by the high carbohydrate content of very-low-fat diets, but in long-term management, this is of little significance.[2] A substantial protein intake (15–17% of energy) permits a lower carbohydrate intake.[5]

Saturated fat intake, in some patients, may increase triglyceride levels, possibly by effecting VLDL metabolism.[1] A reduction in the number of hepatic low-density lipoprotein (LDL) receptors has been proposed, and this may also reduce liver uptake of VLDL remnants. Therefore, saturated fatty acids intake should be reduced to less than 10% of daily energy in the dietary management of hypertriglyceridemia.

The dietary content of polyunsaturated fatty acids is particularly significant in the hypertriglyceridemic subject. When diets rich in fatty acids of the n-6 series (linoleic acid, c18:2,n-6, present in corn oil) are given to hypertriglyceridemic patients, there is frequently an increase in the fecal excretion of cholesterol and bile acids; a well-known reduction in serum cholesterol also occurs.[2] Linoleic acid feeding also lowers triglycerides, although this is not a universal response. In any case, the substitution of linoleic acid for saturated fatty acids is recommended for the dietary treatment of hypertriglyceridemia. Monounsaturated fatty acids will probably serve the same purpose, and they do not have several of the potential disadvantages of high intakes of linoleic acid.

Polyunsaturated fatty acids of the n-3 series (fish oils) have been shown to reduce significantly hypertriglyceridemia in hyperlipidemic phenotypes IIb, III, IV and V. Their hypotriglyceridemic action is dose dependent and is explained by a marked reduction of the hepatic synthesis of VLDL–triglycerides.[6] Thus, consumption of fish, which contain high amounts of n-3 long-chain fatty acids, may have a therapeutic benefit in patients with hypertriglyceridemia and is recommended as a source of fat in their diet. In severe hypertriglyceridemias (i.e., type V hyperlipidemia), the use of fish oil capsules has been successfully employed for reducing excess levels of chylomicrons. The optimal dosage, however, remains unknown.[7]

In some diabetic patients with hypertriglyceridemia, the administration of fish oil capsules has impaired diabetic control and increased LDL and

TABLE V Lipid-Lowering Diet

	Advisable	In Moderation	Not Advised
Fats	All fats should be limited.	Oils or margarine labeled "high in polyunsaturates." Sunflower oil, corn oil, soya oil, safflower oil, olive oil, cottonseed oil. Low fat spreads.	Butter, meat drippings, lard, suet, palm oil, coconut oil, margarines not labeled "high in polyunsaturates," cooking or vegetable oil of unknown origin. Hydrogenated fats and oils.
Meat	Chicken, turkey, veal, rabbit, game.	Lean beef, bacon, ham, pork, lamb, lean mince meat, good quality burgers, liver and kidney.	Visible fat on meat (including crackling), breast of lamb, pork bellies, streaky bacon, sausages, salami, pate, luncheon meat, scotch egg, duck, goose, pork pies, meat pastries. Skin on poultry.
Dairy products	Skimmed milk; low-fat cheeses: eg, cottage cheese, quark (skimmed milk soft cheese), curd cheese; egg whites; low-fat yoghurt.	Semi-skimmed milk. Medium-fat cheeses: eg, Edam, Camembert, Gouda, Brie, cheese spreads, processed cheese, Parmesan in small quantities. Half-fat cheeses; 1–3 whole eggs a week.	Full cream milk, evaporated or condensed milk, cream, imitation cream. Full-fat cheeses: eg, Stilton, cheddar, Cheshire, cream cheeses. Full-fat yoghurt.
Fish	All white fish: eg, cod, haddock, plaice; oily fish: eg, herring, mackerel, sardines, tuna, salmon.	Fish fried in suitable oil, shellfish.	Fish roe.
Fruits and vegetables	All fresh and frozen vegetables: Peas, beans, sweet corn, dried beans of all kinds (eg, haricot, red kidney, butter beans, lentils, chick peas) are particularly high in "soluble fiber"; jacket or boiled potatoes (eat skins wherever possible); fresh fruit, unsweetened tinned fruit, dried fruit.	Chips and roast potatoes if cooked in suitable polyunsaturated fat. Avocado pears, fruit in syrup, crystallized fruit.	Chips or roast potatoes cooked in unsuitable oil or fat. Oven chips. Potato crisps.
Nuts	Walnuts, chestnuts.	Almonds, brazil nuts, hazelnuts.	Coconut.
Cereal foods	Wholemeal flour, wholemeal bread, wholegrain cereals, oatmeal,, cornmeal, porridge, oats, sweet corn, wholegrain rice, pasta, crispbreads, oatcakes, matzos.	White flour, white bread, sugary breakfast cereals, white rice & pasta, plain semi-sweet biscuits, water biscuits.	Fancy breads: eg, croissants, brioche, savoury cheese biscuits, bought pastry.
Prepared foods	Low-fat puddings: eg, jelly, sorbet, skimmed milk pudding, low-fat yoghurt, low-fat sauces.	Cakes, pastry, puddings, biscuits, and sauces made with suitable margarine or oil. Home-made snacks made with polyunsaturated fat.	Cakes and pastry puddings and biscuits made with saturated fats. Suet dumplings and puddings, butter and cream sauces. All proprietary puddings and sauces. Deep-fried snacks. Dairy icecream.
Beverages	Tea, coffee, mineral water, slimline or sugar-free soft drinks, unsweetened fruit juice. Clear soups, home-made vegetable soup. Low-alcohol beer.	Sweet soft drinks, low-fat malted drinks or low-fat drinking chocolate, occasionally. Packet soups, meat soups, alcohol.	Irish coffee. Full-fat malted drinks, drinking chocolate. Cream soups.
Preserves, spreads, sweets	Clear pickles. Sugar-free sweeteners: eg, saccharine tablets or liquid aspartame sweetener.	Sweet pickles and chutney, jam, marmalade, honey, syrup, marzipan, peanut butter and lemon curd. Boiled sweets, pastilles, peppermints, sugar, sorbitol, glucose, fructose.	Chocolate spreads, mincemeat containing suet. Toffees, fudge, butterscotch, chocolate, coconut bars.
Miscellaneous	Herbs, spices, mustard, pepper, vinegar. Low-fat dressings: eg, lemon or low-fat yoghurt.	Meat and fish pastes. Low-calorie salad cream or low-calorie mayonnaise, bottled sauces. French dressing, sparingly. Soy sauce.	Ordinary salad cream, mayonnaise, cream or cream cheese dressings.

See References 4 and 5.

(1) '*Advisable*' foods are generally low in fat and/or high in fibre. These should be used regularly as part of the diet. (2) Foods listed under '*in moderation*' contain polyunsaturated fats or smaller quantities of saturated fats. As diet should be low in fat, these foods are allowed only in moderation. For example: (a) red meat not more than 3 times week^{-1}; (b) medium fat cheeses and meat and fish pastes once a week; (c) homemade cake, biscuits and pastries made with suitable polyunsaturated margarine or oil twice a week; and (d) chips or roast potatoes cooked in suitable oil once a fortnight. (3) Foods '*not advised*' contain large proportions of saturated fats and, therefore, should be avoided wherever possible.

apo B levels. Further studies are needed to establish whether fish oils have a role in the treatment of diabetic hypertriglyceridemia. In the meanwhile, there is no reason to curtail the consumption of fish in these patients.[7]

In patients with hypertriglyceridemia of a modest degree, the substitution of polyunsaturated fatty acids with monounsaturated fatty acids (olive oil) is recommended. Olive oil is considered an adequate dietary fat supplement in hyperlipidemic patients since it allows a reduction in the diet's proportion of daily carbohydrates.[2]

Dietary carbohydrates, in large amounts, stimulate the synthesis of triglycerides in the liver and promote the secretion of triglyceride-rich VLDL. In normal subjects, the rise in triglycerides is relatively small, but in patients who already have hypertriglyceridemia, the rise in serum triglycerides can be marked.[1–2] There is a disagreement in the literature on whether this rise is transient or long lasting. Several clinical trials suggest that it may be transient,[8] but epidemiologic studies indicate that triglyceride levels in populations consuming large amounts of carbohydrate tend to be higher than in populations on low-carbohydrate, high-fat diets. Therefore, the most desirable diet for hypertriglyceridemic patients has not been determined. The generally recommended diet for such patients is a diet containing 30% of calories as fat. The diet preferably should contain complex carbohydrates rich in undigestible fiber (pectin, cellulose, etc.) present in large amounts in alimentary vegetables (Table V). This will reduce caloric intake and thus will help to lower triglyceride levels. Alternatively, if hypertriglyceridemic patients are not obese, the diet can be somewhat richer in unsaturated fatty acids; in a higher fat diet, saturated fatty acids should be restricted.

Alcohol stimulates the formation of triglycerides in the liver and raises the triglyceride content of VLDL. In patients with defective clearance of plasma triglycerides, alcohol induces a marked hypertriglyceridemic response. The effects of alcohol to stimulate the secretion of VLDL–triglycerides are more pronounced in obese subjects than in lean; thus, obese subjects are more likely to develop hypertriglyceridemia on high intakes of alcohol. Therefore, alcohol should be reduced (to <25 g/day) or discouraged in hypertriglyceridemic patients.[5]

CONCLUSION

Dietary therapy is the cornerstone of any treatment regimen for hypertriglyceridemia. Caloric, total fat, saturated fat, and alcohol consumption should be closely monitored. In general, a diet containing 30% of calories as fat and 50–60% as carbohydrate, including complex carbohydrates rich in fiber, is desirable for the control of hypertriglyceridemia. Also, saturated fats should be replaced with monounsaturated and polyunsaturated fats, the latter two having been shown to reduce hypertriglyceridemia.

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C. OTHER NONPHARMACOLOGIC APPROACHES

T. Miettinen, MD, and M. Mancini, MD (Reviewer)

This chapter highlights studies in which nonpharmacologic (and nondietary) approaches are used to normalize elevated serum triglyceride levels. Since the metabolism of triglyceride-rich lipoproteins is associated with lipoprotein lipase activity and the subsequent formation of high-density lipoproteins (HDL), some aspects of these variables are also reviewed in this chapter.[1]

Physical activity, weight reduction, and control of smoking are the most important nonpharmacologic ways to reduce cardiovascular disease (CVD) by normalizing triglyceridemia and HDL levels.[2,3] Partial ileal bypass, porta-caval shunt operations, or low-density lipoprotein (LDL) apheresis, although effective in lowering LDL, are less suitable for the treatment of pure hypertriglyceridemia.

Plasma triglyceride levels are lower in endurance-trained individuals than in sedentary individuals. Physical exercise lowers serum triglyceride levels both after acute exercise and prolonged training. At the same time, exercise increases the activity of lipoprotein lipase, raises the level of HDL (especially of antiatherogenic HDL_2) and reduces the activity of hepatic lipase. These reactions reflect the well-known negative association between triglyceride-rich lipoprotein and HDL levels. In fact, the removal of exogenous triglycerides from plasma is also increased after prolonged exercise.

Experimental studies have also shown that lipoprotein lipase activity of the trained knee extensor muscle is higher than that of the nontrained muscle.[4] The latter muscle also removes less very-low-density lipoprotein (VLDL) triglyceride. The favorable effect of training or physical activity on triglycerides may not depend solely on the enhanced utilization of fatty acids by the trained muscle for energy production from VLDL triglycerides. It may also stem from reduced hepatic VLDL synthesis.[5] In prospective studies, mild-to-moderate, long-term physical activity has been shown to lower effectively serum triglycerides in initially inactive men.[6] All these findings indicate the beneficial effects of physical training on triglyceride-rich lipoproteins and HDL metabolism.

In obese, hypertriglyceridemic subjects, body-weight reduction is a primary goal.[7,8] As the body weight drops, so do VLDL and triglyceride levels, while HDL levels rise. At the same time, the triglyceride content of LDL and HDL decreases. During acute weight reduction, VLDL synthesis and lipoprotein lipase activities are decreased, VLDL removal is enhanced, and HDL levels may increase. During weight stabilization at a lower level, the kinetic parameters of VLDL appear to remain improved, while lipoprotein lipase activity in adipocytes may stay elevated and HDL levels are normalized.[9-12]

A recent comparison of weight reduction by diet and exercise showed that both measures significantly reduce serum triglyceride levels, while increasing HDL levels.[13] These changes may be detectable to a greater degree in hypertriglyceridemic subjects with abdominal obesity.[14,15] Since weight reduction alone may not be successful in all overweight hypertriglyceridemic subjects, a combination of dietary arrangements with enhanced physical activity is recommended.

Smoking greatly enhances the risk of coronary heart disease (CHD) in patients with other coronary risk factors. Indeed, epidemiologic studies have shown that compared with mean normal values, smokers have significantly higher serum concentrations of cholesterol (3.0%), triglycerides (9.1%), VLDL (10.4%), and LDL (1.7%), and lower levels of HDL (−5.7%) and apolipoprotein A-I (−4.2%).[3] Smokers also have a greater degree of catecholamine-induced lipolysis and enhanced adipose tissue lipoprotein lipase activity. Smoking cessation reverses these trends but also stimulates the appetite. Most smokers who quit experience a temporary weight gain. This increase in body weight may be related to adipose tissue lipoprotein lipase activity, which may temporarily increase after smoking cessation.[16,17] Weight gain, if not controlled carefully, can markedly impair the lipoprotein profile, especially in hypertriglyceridemic subjects.

CONCLUSION

Several nonpharmacologic measures can be implemented, with dietary therapy, to treat hypertriglyceridemia. These include regular physical activity, weight reduction, and smoking cessation.

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D. PHARMACOLOGIC MANAGEMENT OF HYPERTRIGLYCERIDEMIC PATIENTS

G. Franceschini, MD, and L. A. Carlson, MD (Reviewer)

Drug therapy in hypertriglyceridemia is justified only when the modifications of dietary and lifestyle habits fail to correct the abnormalities in the lipid/lipoprotein pattern. Drugs may also be required to reduce the concomitantly elevated cholesterol levels in familial combined hyperlipidemia or dysbetalipoproteinemia.

Clinical trials aimed at evaluating the effect of treatment on cardiovascular morbidity and mortality in hypertriglyceridemic patients are lacking. However, subgroup analysis of data from the Helsinki Heart Study[1] demonstrates that the reduction of coronary heart disease (CHD) incidence was largest in type IIb patients. Furthermore, in the Stockholm IHD Study, a secondary prevention trial, the combined use of clofibrate and nicotinic acid reduced the 5-year mortality by 26%. Two observations supported the beneficial effect of triglyceride lowering: (1) reduction of mortality only occurred in myocardial infarction survivors with a triglyceride level above 1.5 mmol/L, and (2) the reduction in mortality was greater the more the triglycerides were lowered.[2] It thus appears that drugs might be useful in an attempt to retard the progression of atherosclerosis in hypertriglyceridemic patients.

Drug therapy for patients with severe hypertriglyceridemia may also eliminate the risk of pancreatitis. However, lipid-lowering drugs are of little value in subjects with familial lipoprotein lipase or apo C-II deficiencies. These subjects generally respond only to a low fat diet.

FIBRATES

The name "fibrates" includes a family of drugs derived from the parent compound clofibrate. All of the fibrates are characterized by an aryloxy group but with different substituents. Bezafibrate and fenofibrate have a Cl substituent at the para position on the aromatic ring; gemfibrozil has a 2.5-xylyloxy group.

In spite of their considerable chemical similarities, the various fibrates differ strikingly in their pharmacokinetic behavior. The elimination half-life in healthy volunteers ranges between 1.5 and 2 hours for gemfibrozil and bezafibrate to more than 20 hours for clofibrate and fenofibrate. In the case of newer derivatives, the pharmacokinetic differences dictate the dosage regimens: 250–300 mg/day for fenofibrate; 400–600 mg/day for bezafibrate; 900–1,200 mg/day for gemfibrozil and 1,500–2,000 mg/day for clofibrate.

All the fibrates are highly effective in reducing plasma triglyceride and very-low-density lipoprotein (VLDL) levels. In addition to triglyceride lowering, fibrate treatment corrects, although to a variable degree, many of the lipoprotein abnormalities associated with the hypertriglyceridemic state. In general, bezafibrate and fenofibrate are more effective in the treatment of primary hypercholesterolemia than are gemfibrozil or clofibrate.[3] Accordingly, low-density lipoprotein (LDL) concentrations are reduced in patients with mixed hyperlipidemia to different degrees by the different fibrates, while LDL cholesterol can also increase in patients with severe primary hypertriglyceridemia and familial dysbetalipoproteinemia, when a massive drop of the triglyceride level is achieved. However, the altered composition and structure of LDL is normalized, and their capacity to interact with the LDL receptor is fully restored.[4] Plasma high-density lipoprotein (HDL) levels markedly increase, the rise being generally confined to the HDL$_3$ subfraction, which is the preferred acceptor of cellular cholesterol.

The mechanism by which fibrates exert their effect on plasma lipoproteins is most likely related to an increased catabolism of the triglyceride-rich lipoproteins.[5] A stimulation of lipoprotein lipase activity has been repeatedly demonstrated after treatment with the various compounds. The response of hepatic lipase is more variable. Whether

Primary Drugs For Treatment of Hypertriglyceridemia

Fibric acid derivatives:
- gemfibrozil
- bezafibrate*
- fenofibrate*
- ciprofibrate*

Nicotinic acid and derivatives

*Not yet approved by the United States Food and Drug Administration

the increase in lipoprotein lipase activity is due to a direct effect of fibrates on enzyme synthesis or to a better utilization of the lipoprotein substrate by the existing enzyme is unknown.

Changes in plasma triglyceride and VLDL levels following fibrate treatment are generally correlated with the increase in lipoprotein lipase activity, thus confirming the major effect of fibrates on VLDL catabolism. These compounds, however, can also be effective in decreasing VLDL–triglyceride (but not VLDL apo B) production.[6] It thus appears that they are indicated as treatment of choice for patients with both types of primary hypertriglyceridemias: VLDL overproducers and VLDL hypocatabolizers. Fibrates are the drugs of choice for patients with dysbetalipoproteinemia. In these patients, the defect in VLDL catabolism is corrected in three ways: by the reduction and sometimes even disappearance of β-VLDL from plasma; by the regression of xanthomas; and by possible improvements in the vascular conditions. Fibrates can also be used in the treatment of mixed hyperlipidemia. In this syndrome, the association of fibrate with a pure cholesterol-lowering drug may enhance the cholesterol-lowering effect.[7]

Long-term studies with the various fibric acids generally reported an extremely low incidence of side effects. An increased risk for gallstone formation has been detected in earlier large trials with clofibrate,[8] but not confirmed in the more recent Helsinki Heart Study[1] with a second-generation fibrate. Painful muscles were sometimes associated with increased creatinine phosphokinase values, while alterations of liver enzymes are generally transient and do not lead to clinically evident liver damage. In diabetics, glucose tolerance often improves independently from the hypolipidemic effect. Furthermore, bezafibrate and fenofibrate lower elevated fibrinogen levels.

NICOTINIC ACID AND DERIVATIVES

Nicotinic acid is a powerful triglyceride-lowering drug.[9] Unfortunately, due to a variety of subjective and objective side effects (flushing, itching in the face), it is seldom prescribed, particularly in warmer climates. A treatment schedule minimizing side effects starts with low doses (0.25 g, 3–4 times daily) slowly increasing up to 4 g/day or more. The administration of a 0.5-g aspirin tablet half an hour prior to nicotinic acid has also been reported to increase compliance to treatment (aspirin may also raise blood levels of nicotinic acid). Patients with gastritis or peptic ulcer should be treated with particular care, due to a possible worsening of gastric symptoms. Nicotinic acid treatment may also raise uric acid levels (thus precipitating attacks of gout) and impair glucose tolerance. Several nicotinic acid analogues have been developed to improve drug tolerability (acipimox, nicotinyl alcohol, etc.); these analogues also show significant hypotriglyceridemic activity.

Nicotinic acid is a potent antilipolytic drug, decreasing lipid mobilization from adipose tissue.[9] This effect is probably responsible for the reported inhibition of VLDL secretion by the liver, resulting in a decreased number of circulating VLDL and LDL particles. Consequently, nicotinic acid can be expected to lower triglyceride levels most effectively in patients with VLDL overproduction. Similarly to other triglyceride-lowering agents, the composition and receptor affinity of LDL is also normalized by nicotinic acid derivatives in hypertriglyceridemic patients.[10] Moreover, the drug and its derivatives increase plasma HDL levels, possibly through an inhibition of hepatic lipase. These changes in the lipid/lipoprotein pattern have been recently associated with a significant reduction of mortality from all causes in a 15-year follow-up of the Coronary Drug Project patients.[11] Furthermore, when associated with an anion exchange resin, nicotinic acid treatment led to a significant regression of atherosclerosis in coronary bypass patients.[12]

Nicotinic acid and its analogues are recommended for patients with mixed hyperlipidemia, in whom the drug reduces both cholesterol and triglyceride levels. Patients with primary hypertriglyceridemia due to VLDL overproduction should also benefit from this treatment. Nicotinic acid, like fibrates, is also highly effective in type V hyperlipoproteinemia, where triglyceride levels can be lowered from 1,700–4,000 mg/dL to about 400 mg/dL, thereby abolishing the recurrent attacks of pancreatitis.

OTHER HYPOTRIGLYCERIDEMIC DRUGS

Other treatment options for hypertriglyceridemic patients include the use of metformin and fish-oil supplementation (see Chapter 7B). Pure hypocholesterolemic drugs such as anion exchange resins (which may often increase plasma triglyceride levels) should be avoided. Although HMG-CoA reductase inhibitors are mainly indicated to hypercholesterolemic patients, they also reduce triglycerides by 15–20% and appear to be effective in the treatment of mixed hyperlipidemia and diabetic hypertriglyceridemia,[7,13] where they have been used alone or in combination with gemfibrozil. This combination carries an increased risk of myositis. Also, direct inhibition of cholesterol synthesis by these agents may lead to secretion of VLDL depleted in cholesterol.

Metformin, an antidiabetic biguanide with hypotriglyceridemic activity,[14] is particularly useful in the treatment of patients with diabetes or with a reduced carbohydrate tolerance.[15] Metformin may also improve peripheral insulin activity and reduce plasma PAI-1 levels.

CONCLUSION

Subgroup analysis of several clinical trials, including the Helsinki Heart Study, have demonstrated that pharmacologic agents can successfully improve patients' lipid profiles, including their triglyceride levels, and thus reduce their risk for CHD. Fibric acid derivatives and nicotinic acid are currently the drugs of choice when treating hypertriglyceridemic patients.

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NOVEMBER 4, 1991

A Symposium: Mechanisms of Myocardial Ischemia and Injury in Unstable Angina Pectoris

GUEST EDITOR:
James S. Forrester, MD
Professor of Medicine
UCLA School of Medicine
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Cedars-Sinai Medical Center
Los Angeles, California

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The American Journal of Cardiology®

Introduction

James S. Forrester, MD

This symposium aims to integrate basic and clinical studies in the field of vascular biology. It progresses from the functions of the normal endothelial cell to the vascular response to injury, to the pathophysiology and management of acute coronary syndromes Although we cannot claim to be comprehensive, we can claim to be au courant: the time from speakers' presentations to publication is only about half a year.

We begin with an overview of the new field of cardiovascular molecular biology by Robert Roberts. In decades to come, the resolution of unstable angina and acute myocardial syndromes may lie in studies outlined by Roberts. It will be possible to design agents with desirable domains while eliminating specific domains not required for the patient under care. This idea holds unlimited promise, not only for cardiology, but for the entire field of clinical medicine.

To begin our exploration of vascular biology, Elizabeth Nabel describes the normal and abnormal function of the endothelial cell. Nabel sees the endothelial cell as a regulatory organ with four functions: hemostasis, contractility, proliferation, and inflammation. The role of endothelial hemostasis in atherosclerotic lesions has long been recognized. Less well understood is the part played by contractility, particularly as modulated by endothelium-derived relaxing factor (EDRF) and its effect on the reactivity of the vessel that has an intact surface versus one that has not. EDRF is closely allied to nitrous oxide and has an action analogous to that of nitroglycerin. Other compounds that contribute to smooth muscle contractility are the vasodilator prostaglandin I_2 (prostacyclin) and the newly identified substance endothelin, a potent vasoconstrictor produced by the endothelial cell. Nabel also describes the action of the endothelial cell in stimulating and suppressing cell proliferation. The endothelium-derived growth factor fibroblast growth factor (FGF) amplifies endothelial cell proliferation, whereas heparin, the most potent natural inhibitor of smooth muscle cell proliferation, is also abundantly secreted by the endothelial cell.

James Chesebro discusses the rheology of shear stress. Platelet aggregation occurs at sites of high shear stress, whereas fibrin is deposited at sites of low shear stress. The presence of thrombin induces the secretion of the vasoconstrictor endothelin, providing the rheostatic mechanism that is crucial to the pathogenesis of acute coronary syndromes, particularly unstable angina. Chesebro's description of the recently synthesized antithrombin agent hirudin gives a tantalizing glimpse of the likely direction of future studies in thrombolytic therapy. In contrast to heparin, hirudin leaves no residual thrombus in animal models. No clinical studies have yet been published, however, and further investigations will be required to determine safety, dosage, and other aspects of therapy.

The pathogenesis of unstable angina has both a physical and a biochemical support. The atherosclerotic lesion is formed when lipid entering the vessel wall is ingested by mesenchymal cells, which become activated to produce growth factors such as platelet-derived growth factor (PDGF) and insulin-like growth factor type 1 (IGF-1)—both potent stimuli to smooth muscle cell proliferation—and transforming growth factor-β (TGF-β), a stimulus to extracellular production. Whereas the process of atheroma breakdown appears to be driven by cytokines, such as tumor necrosis factor and interleukin-1, which cause neovascularization and erosion of the fibrous cap, rupture itself probably occurs through physical disruption, often at the junction of normal and abnormal segments.

These observations suggest that 3 aspects of therapy ought to be considered: inhibition of platelet aggregation, inhibition of thrombus formation, and vasodilation. Properly implemented, this therapy should achieve the 3 clinical goals in the management of unstable angina: (1) decreasing the risk of myocardial infarction, (2) preventing subsequent development or recurrence of angina, and (3) attenuating risk factors. David Waters and colleagues have found in broad-scale studies that heparin and aspirin both effectively inhibit platelet aggregation. It is not clear that the two agents given in combination are more effective than either given alone, although data from Sweden indicate that this may be the case.

Two authors provide a European perspective. Semi Sen describes treatment of acute myocardial infarction in Germany. Serge Degré presents an important comparison of nitroglycerin versus the calcium antagonist diltiazem in which, after 48 hours of treatment, 100% of nitroglycerin-treated patients compared with only 11% of diltiazem-treated patients still had ST-segment depression and silent ischemia. This striking difference may have been derived in part from diltiazem's beneficial effect on heart rate, and in part from tolerance to nitroglycerin.

Thomas Heywood describes the biphasic reponse of calcium antagonists in terms of left ventricular function. Allan Ross discusses balloon angioplasty, which, in some centers, has become the treatment of choice in unstable angina, despite a relatively high rate of complications. The rate of restenosis (57% at 6 months postangioplasty) suggests that much is to be gained from refinement of pharmacologic approaches. Robert Feldman describes current modes of ancillary therapy for unstable angina.

Neal Kleiman and Prediman K. Shah review unresolved issues in thrombolytic therapy, noting that the GISSI trial has permanently modified practitioners' views of treatment for acute myocardial infarction. Kleiman notes that the timing of thrombolytic therapy is crucial to outcome; Shah presents a persuasive viewpoint on aspects of late reperfusion.

In summary, we describe an imaginative understanding of the pathogenesis of unstable angina at the level of the cytokines and growth factors expressed by macrophages and other mesenchymal cells. This understanding has extended to the pathophysiology of unstable angina, as expressed through the interaction between blood elements, the vessel wall, and vasoactive substances. This basic science provides a strong foundation for clinical intervention, and for the prospect of important advances in the management of unstable angina in the decade ahead.

Molecular Biology and Its Impact for the Future

Robert Roberts, MD

Over the past few decades, physicians have watched cardiovascular disease therapy move from largely empiric to more sophisticated treatments based on physiologic principles and, more recently, molecular biology. Cardiology has been slower than other disciplines to move into the arena. Aspects of molecular genetics are nearly 4 decades old, dating from the 1940s, including the classic experiments of Watson and Crick on the structure and function of deoxyribonucleic acid (DNA). In much the same manner as cardiology demystified hemodynamics in the 1960s and 1970s and incorporated its principles into everyday practice, the near future will see the use of the molecular biologic techniques that are fundamental to all disciplines of medicine and industry.

MOLECULAR BIOLOGY: THE VERY BASICS

The terminology of molecular cardiology will probably become familiar to both academicians and practitioners within a few years. Research has increased our understanding of cardiac muscle disease; regulation of intracellular ions; myocardial injury; cardiac growth and regulation of gene expression; endocrine functions of the heart; blood vessel–endothelium interaction; and regulation of vascular tone, atherosclerosis, and thrombolysis.[1] The study begins with an understanding of DNA, a huge molecule composed of monotonously repeating combinations of 4 base pairs. Although the problem can be simply stated, the task is formidable, since the amount of DNA in a single cell carries enough genetic information to fill a book of 1 million pages. Put another way, if all the DNA molecules in one person were placed end-to-end, the resulting chain would reach from Earth to the moon 8,000 times. One cell contains 3 billion base pairs, enough to code for 10 million genes. DNA is "selfish," since less than 1% appears to participate in protein generation; the human genome has between 20,000 and 50,000 genes.

The ability to unravel the enormous maze of DNA came in the 1970s with several Nobel Prize-winning contributions. Early in the decade, it was shown that site-specific recognition and cleavage of DNA were possible by using specific restriction endonucleases that typically recognize 4–6 bases This permitted investigators to know precisely where a DNA molecule had been cut. Since then, more than 300 restriction enzymes have been identified. ("Restriction enzyme" refers to the discovery of enzymes in bacteria that restrict foreign DNA from entering a bacterium's genome by using the bacterial nuclease.)

The next major advance was the discovery of reverse transcriptase. This enzyme allows generation of complementary DNA from a messenger ribonucleic acid (mRNA) isolated from cell cytoplasm. This is the reverse of the usual RNA generation sequence, in which DNA is transcribed into mRNA that is then transported to the cytoplasm. In the presence of a ribosome, the mRNA is translated into protein.

Next, DNA cloning techniques were developed to permit splicing a piece of DNA into a foreign genome with subsequent expression of its product. Thus, the cutting of DNA by means of a site-specific restriction endonuclease and splicing the selected portion into a foreign genome to produce a specific protein were the birth of cloning a recombinant molecule.

Two principal methods are commonly employed for DNA analysis. In restriction fragment length polymorphism (RFLP) analysis, genomic DNA is digested by the bacterial restriction endonuclease, producing fragments that typically range from <1 to >20 kilobases in size. These fragments are separated by agarose electrophoresis and transferred to a support membrane. The fragments of DNA containing the genes to be studied are detected by hybridization with isolated and labeled segments of the cloned gene.[2] A series of 1–6 bands can be used to characterize and fingerprint a haplotype.[3,4] In a modification of this method, a

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synthetic oligonucleotide of about 20 bases is used as the gene probe. For example, this oligonucleotide can be synthesized to match a mutated fragment of a specific coding region.[5]

Recently, investigators have used the technology of the polymerase chain reaction (PCR), which allows direct sequencing of the gene of interest. Theoretically, a "library" of complementary DNAs could be constructed and screened with gene probes to isolate the clone containing the gene of interest, which could then be sequenced. The PCR involves double priming of DNA (or mRNA) and synthesizing multiple copies of the region of the gene between primers.[6] Work is conducted at temperatures higher than body temperature in order to accelerate the reactions. With this method, one can define protein molecules in quantities far smaller than is possible with alternative methods, such as 2-dimensional polyacrylamide gel electrophoresis. Proteins present in small amounts (e.g., tissue plasminogen activators [t-PA]) are readily detected by this method.

MONOCLONAL ANTIBODIES AND CARDIOLOGY

The normal immune system responds to "foreign" substances in a variety of ways, including production of antibodies against multiple antigenic sites, or epitopes, on the offending molecule. The broad range of antibodies produced reflects different antigenic determinants on the foreign substance. Classically, monoclonal antibodies are produced by immunizing a mouse with an antigen. The spleen is harvested and plasma cells are isolated and "immortalized" by fusing them with a myeloma cell line. This process yields a perpetually reproducing hybridoma, which clonally produces an antibody to one of the immunizing antigens.[7]

One problem with this procedure is that it may take up to 18 months to produce products suitable for human use Another problem is the production of human anti-mouse antibodies (HAMAs). Diagnostic monoclonal antibodies (e.g., indium-111–labeled antimyosin to image necrotic myocardium) rarely present a problem, since the half-life is short and, typically, they are administered only once. However, therapeutic monoclonal antibodies (e.g., those used for oncology) may require multiple administrations, with longer in vivo half-lives. To solve this problem, the antigen-binding portion, or F(ab) section, of the HAMA is spliced onto a human antibody. The resulting chimeric monoclonal antibody appears to induce less HAMA production than the nonhumanized antibody.[8]

MOLECULAR BIOLOGY AND THE CLINICIAN

What can be accomplished with the techniques just described? There are 4 broad areas of potential importance: (1) it is now possible to perform in vivo structure–function analysis of a single molecule (or portion thereof) in the intact, living cell or organism; (2) the gene from a particular molecule can be put into a cell culture or into an intact organism to observe its behavior, and genetic engineering can produce mutations of the molecule; (3) diagnostic in situ hybridization can be used to localize DNA or RNA in a biopsy sample (to the cardiologist, this might mean rapid diagnosis of a viral genome in an endomyocardial biopsy specimen); and (4) so-called "designer" biologicals can be generated, for example, mutated forms of recombinant t-PA (rt-PA) that have specific biologic advantages over the naturally occurring product.

Potential applications in thrombolytic therapy: The thrombolytic agents in common use are plasminogen activators that convert the proenzyme plasminogen to the active but nonspecific protease, plasmin. This protease degrades fibrin in blood clots, but also degrades both fibrinogen and other clotting factors (most notably factors V and VIII). During the activation of the fibrinolytic system by plasminogen activators, the circulating inactivator of plasmin, α_2-antiplasmin, is rapidly consumed and bleeding may ensue.

The t-PA molecule is composed of 527 amino acids and includes 16 disulfide bonds. There are 3 glycosylation sites and 5 discrete domains in this molecule. These are, in turn, encoded by 14 exons. More than 40 mutant t-PA forms are currently under investigation to improve the pharmacokinetic profile of this agent. For example, one form being developed contains only the (subunit) kringle 2 and the catalytic site. It has a half-life of 60 minutes, may be given as a single injection, and appears to be equivalent or superior in both potency and fibrin specificity.

In general, several approaches to t-PA modification have been suggested.[8–10] In the example just mentioned, deletion mutation of functional domains modifies drug clearance and fibrin specificity. Higher fibrin specificity may be achieved by mutation of the plasmin cleavage site, which prevents conversion of 1-chain t-PA to 2-chain t-PA. Either glycosylation or active site acylation slows drug clearance. In the latter, this occurs in a manner analogous to that used for anistreplase (anisoylated plasminogen–streptokinase activator complex [APSAC]).

Newer attempts to "target" fibrinolysis have used a monoclonal antifibrin antibody. This agent binds fibrin, but not fibrinogen, with high affinity and may be linked chemically, immunologically, or by recombinant DNA methods to urokinase, rt-PA, or single-chain urokinase plasminogen activator (scu-PA).[7–9] Alternatively, urokinase may be linked to a monoclonal antibody specific for the platelet–fibrinogen receptor complex (glycoprotein IIb/IIIa), yielding enhanced potency with platelet antiaggregant activity.

Other approaches use monoclonal antibodies with specificity for both fibrin and one of the plasminogen activators in order to concentrate the fibrin at the site of the plasminogen activator. The development of chimeric molecules has expanded the field. For example, one such molecule was developed to combine the fibrin affinity of the t-PA with an antibody to macroglobin. However, agents obtained by such exon shuffling have generally been inferior to the parent molecules, possibly because of differences in tertiary structure (protein folding) in comparison to the native molecule.

THE FUTURE: GENETIC ENGINEERING AND HEART FAILURE

A structure–function analysis of cardiac muscle is paramount in properly understanding heart failure. For example, cardiac physiologists have known for decades that cardiac work load is altered by end-diastolic fiber length (Starling's law). On the cellular level, work may be regulated by biochemical changes, the concept of excitation–contraction coupling. Now, this issue can be approached on the molecular level because of confirming evidence that altered gene expression plays a role in the regulation of cardiac function and hypertrophy.[7] In the setting of heart failure, major shifts occur in expressed forms of contractile proteins, sodium–potassium adenosine triphosphatase (Na^+,K^+-ATPase) and other proteins.[11,12] Proto-oncogenes appear to have a role in myocyte proliferation and terminal differentiation and in the regulation of the response to cellular death (as occurs in myocardial infarction).

An example is the isolation of the gene for atrial natriuretic factor. A transgenic mouse may be transfected with atrial natriuretic factor-promoter region DNA that has been linked to an oncogene. The result is massive right atrial hypertrophy and supraventricular arrhythmias.[13]

At present, cardiac therapeutic interventions based on the principles described above are still in the distant future. Study has been hampered by the myocyte resistance to mutation, lack of cell lines in vitro, insufficient neoplasms to study, and difficulty in obtaining adequate tissue serially. Nonetheless, the possibility of specific cardiac gene therapy or the induction of cardiac myocyte replication is now within reach.

Indeed, today more than 80 drugs are produced by genetic engineering, with a major increase predicted over the next decade. The future holds great promise for molecular genetics and molecular cardiology, with major diagnostic and therapeutic advances just around the corner.

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Biology of the Impaired Endothelium

Elizabeth G. Nabel, MD

The endothelium is a regulatory organ that mediates hemostasis, contractility, cellular proliferation, and inflammatory mechanisms in the vessel wall. Injury to the endothelium from hypertension, smoking, hyperlipidemia, and diabetes mellitus disrupts normal regulatory properties and results in abnormal endothelial cell function. Clinically, endothelial cell dysfunction can be manifested as vasospasm, thrombus formation, atherosclerosis or restenosis. The normal hemostatic properties of the endothelium include the maintenance of a nonadhesive luminal surface, antithrombotic properties, anticoagulant properties, and fibrinolytic properties. The endothelial cell regulates smooth muscle cell contractility by the production of relaxing and constricting factors in response to physiologic stimuli. Endothelial cell injury is also an initial event in the development of atherosclcrosis and restenosis by facilitating platelet adhesion and aggregation and by signaling the release of mitogens from platelets, macrophages, and endothelial cells, which stimulate smooth muscle cell proliferation. In addition, endothelial cells undergo morphologic and functional alterations in response to cytokine signals, which may contribute to the pathogenesis of vasculitis and atherosclerosis. In sum, the normal endothelium performs many regulatory functions which become altered when the endothelium is injured.

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The normal endothelium maintains a nonadhesive luminal surface and has fibrinolytic, anticoagulant, and antithrombotic properties [1,2]. A normal endothelial surface prevents the attachment of platelets. Platelet aggregation and adhesion are also normally inhibited by endothelial cell synthesis of prostacyclin (prostaglandin I_2) and endothelium-derived relaxing factor (EDRF) [3,4]. Antithrombotic and fibrinolytic properties of the endothelium are regulated by basal synthesis of tissue-type plasminogen activator (t-PA), which stimulates lysis of fibrin clots. Antithrombotic properties in the vessel wall are regulated through synthesis of antithrombin III, which binds to and inactivates thrombin, factor X, and other serine proteases [5]. Anticoagulant properties in the vessel wall are regulated by several pathways. The principal anticoagulant action of the endothelium is mediated through protein C and protein S [6]. The binding of thrombin to thrombomodulin serves to activate protein C; the latter, in turn, blocks factors Va and VIIIa. Antithrombin III inactivates thrombin and factor Xa, as well as endothelial cell serine proteases. The thrombin–thrombomodulin complex inactivates the procoagulant properties of thrombin, such as platelet activation. In addition, endothelial cell production of heparin-like glycosaminoglycans catalyzes the inactivation of coagulation proteases such as thrombin and factor X [7].

HEMOSTASIS

Normal hemostasis is disrupted when the vessel is injured. Subendothelial (collagen matrix) basement membrane is exposed. von Willebrand's factor is activated by thrombin to facilitate platelet adhesion and aggregation. Platelet-activating factor also contributes to primary hemostasis. Endogenous thrombolysis (t-PA) is inhibited by plasminogen activator inhibitor. Endothelial cell disruption also exposes tissue factor VII, which activates the extrinsic coagulation pathway, as well as factor XII, which stimulates the intrinsic coagulation pathway. Endothelial cell serine proteases also facilitate thrombus formation.

Endothelial cell injury stimulates primary hemo-

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stasis by several mechanisms. Platelet adhesion occurs when platelets bind to the subendothelium via the platelet collagen receptor glycoprotein IA and to basement membrane by interactions with von Willebrand's factor and the glycoprotein IB receptor. Platelet aggregation follows when platelets bind to other platelets via the platelet glycoprotein receptor IIB IIIA. Platelet degranulation results in the release of vasoactive proteins from α granules, such as adenosine diphosphate (ADP), serotonin, thromboxane A_2, thrombin, and histamine, which further promote platelet aggregation, vasoconstriction, leukocyte chemostasis, and formation of a hemostatic plug.

CONTRACTILITY

The healthy endothelium regulates vascular contractility and promotes vascular relaxation. The endothelium contains receptors for various pharmacologic stimuli, including thrombin, vasopressin, acetylcholine, and platelet granulation products [8]. Receptor binding stimulates endothelial cell synthesis and release of EDRF, which acts locally on smooth muscle cells to stimulate production of cyclic guanosine monophosphate (cGMP) which, in turn, mediates relaxation [9]. Although more investigation is needed, there is convincing evidence that EDRF encompasses a group of substances, one of which is probably nitrous oxide [9,10]. Other non-receptor-mediated stimuli, such as shear stress and calcium ionophore, also initiate EDRF release [11]. Endothelial cells promote smooth muscle cell relaxation through the local production of prostacyclin which causes an increase in cyclic adenosine monophosphate (cAMP), resulting in vasodilation.

These vasodilator mechanisms are counterbalanced by vasoconstrictor substances produced by the endothelium. For example, endothelin is a potent vasoconstrictor produced by the endothelial cells in response to hypoxia and other stimuli [12]. The exact physiologic role of endothelin in normal and atherosclerotic conditions is now under evaluation.

A complex series of events occurs when the endothelium is injured. Since receptor-mediated stimulation of EDRF is disrupted, physiologic and pharmacologic stimuli produce a direct effect on smooth muscle cells, resulting in vasoconstriction. For example, vasoconstriction is routinely observed following coronary angioplasty [13]. Vasospasm surrounding an atherosclerotic plaque may occur due to deficient release of EDRF, and probably accounts for some angina experienced by patients with coronary artery disease.

CELLULAR PROLIFERATION

Injury to the endothelium may initiate the development of atherosclerosis [14]. Circulating monocytes adhere to the injured vessel surface and migrate into the intima, take up extracellular lipid as macrophages, and develop into foam cells. Growth factors, released by platelets, endothelial cells, and macrophages, promote smooth muscle cell migration into the intima and proliferation. Macrophages and proliferating smooth muscle cells engage in collagen matrix synthesis. Abnormal cellular proliferation, in combination with calcium deposition and thrombus formation, results in the development of an atherosclerotic plaque. Balloon injury following angioplasty initiates a similar process of pathologic cellular proliferation, which becomes manifest over several months as restenosis [15]. Release of mitogens by activated endothelium, platelets, and mononuclear cells may be associated with a change in medial smooth muscle cells. The smooth muscle cell is normally refractory to growth factors and does not synthesize collagen matrix. When the blood vessel is injured, the smooth muscle cell may undergo a 'phenotypic' change to a synthetic cell where it becomes noncontractile, responsive to growth factors, and capable of connective tissue synthesis [16].

IMMUNITY AND INFLAMMATION

The endothelium is responsive to a number of cytokines, including the interferons (α, β, and λ), tumor necrosis factor-α, interleukin-1, and interleukin-6 [17]. These products of the immune system can induce changes in endothelial cell structure and function by a process termed endothelial activation. Endothelial cells become activated by the binding of leukocytes, monocytes, and lymphocytes to the endothelium by adhesion molecules. For example, interleukin-1 can induce the synthesis of endothelial leukocyte adhesion molecule-1 (ELAM-1), which stimulates neutrophil adhesion to endothelial cells [18]. Interferon-λ stimulates intracellular adhesion molecule 1 (ICAM-1) expression, which in turn promotes lymphocyte attachment and a local immune response. The adhesion of mononuclear cells to endothelial cells by adhesion molecules is a process that is central to vascular inflammation and a response to immune injury [19,20]. These mechanisms may also be responsible, in part, for the accelerated atherosclerosis observed in cardiac transplant arteries.

In conclusion, the endothelium is a highly active and reactive tissue that regulates hemostasis, vascular contractility, cellular proliferation, and immunity and inflammation. As our understanding of the endothelium expands, new therapeutic modalities are likely to emerge, based on recombinant DNA technology [21,22].

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Plaque Disruption and Thrombosis in Unstable Angina Pectoris

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Therapeutic strategies and clinical trials in unstable angina should be based on the pathogenesis, risk, and mechanisms of thrombosis. The mechanisms of thrombosis and the differences in the effects of anticoagulant, antithrombotic, antifibrin, and antiplatelet drugs must be taken into account when determining the dosage and duration of therapy. Ignoring these principles may prevent identification of new therapy, increase the cost of new drug development and research, increase the cost of new drugs, and increase the cost of medical care.

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Mechanisms of thrombosis involve plaque disruption, mural thrombosis due to local substrates, systemic factors, rheology of blood flow, vasoconstriction associated with arterial injury, and the accumulation of an additional, very thrombogenic local substrate, mural thrombus. Mechanisms of the acute coronary syndromes and coronary disease progression have recently been reviewed.[1]

PLAQUE DISRUPTION

The acute coronary syndromes of unstable angina, acute myocardial infarction, and sudden cardiac death have a common underlying pathology of plaque disruption in approximately three fourths of cases. Endothelial denudation with an associated stenosis and platelet aggregate may be present in the remaining one fourth.[2–4] Plaques that are prone to rupture contain a pool of extracellular cholesterol within an area of fibrous thickening. Fissuring may result from circumferential tensile stress on the thinned cap of fibrous tissue covering the soft lipid core, weakening of the cap by an infiltrate of macrophages (initially attracted by lipids and thus often containing lipids), and external shear forces within the arterial lumen.[4,5] Fissuring occurs most often at the margin of the fibrous cap where a thick layer of collagen has dissolved into a delicate latticework that is prone to disruption. After disruption, flowing blood contacts local substrates in the arterial wall within the fissure, which anchors the growing thrombus. Some thrombi are small and remain localized within the fissure without extending into the lumen; these may result not in clinical symptoms but merely in an increase in the bulk and size of a plaque with asymptomatic progression of disease. Others extend into the lumen, continue to grow in size, and may reduce blood flow, causing symptoms of ischemia or progress to total occlusion, often with the development of acute myocardial infarction.[6,7] In patients who have died from the acute coronary syndrome, the thrombus at the site of the ruptured plaque most often is layered due to evolution at different

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times. This suggests a potential for preventing myocardial infarction and death and reducing the need for coronary revascularization if patients with unstable angina can be treated early with antithrombotic therapy which totally blocks growth of mural thrombus. Complete inhibition of thrombosis may also allow endogenous thrombolysis to dissolve the mural thrombus and markedly reduce the obstruction to blood flow. As will be discussed, the obstruction to blood flow is often very minor (<50% stenosis) prior to plaque disruption.

Atherosclerotic arteries often have a variety of vascular injuries, including type I injury (nondenuding dysfunctional endothelium), which appears to produce lesser amounts of endothelium-derived relaxing factors (EDRF). Thus these arteries are prone to focal vasoconstriction or spasm. Focal areas of atherosclerotic arteries may also contain type II injury (denuding endothelial injury without medial damage), which may attract a single layer of platelets or, intermittently, an aggregate of platelets, especially when associated with a focal stenosis. Fissuring of a plaque is an example of type III or deep injury (endothelial denudation plus injury into the media or deep into the plaque), which leads to acute platelet deposition within seconds and possible progression to acute occlusion within minutes.[8–10]

MURAL THROMBOSIS

Three major factors contribute to arterial thrombosis: (1) local arterial substrates, (2) systemic factors, and (3) the rheology of blood flow.

Local arterial substrates: Local substrates within the arterial wall vary with the depth of injury. The subendothelium contains less thrombogenic types of collagen (types IV and V) whereas medial tissue or plaque contains more thrombogenic collagens (types I and III).[11,12] Tissue thromboplastin initiates thrombosis and is especially rich within the adventitia of even normal arteries and is found within the fibrous cap of the plaque and variably within the arterial media.[13,14] The in vivo role of tissue factor has been demonstrated by the use of antibodies to tissue factor in enhancing arterial patency of the inverted (inside-out) femoral artery in rabbits.[15] Endothelium protects against thrombosis in part by the production of prostacyclin and EDRF. Both of these substances have potent antiplatelet properties. Prostacyclin is also synthesized by arterial structures adjacent to the lumen. Thus, arterial injury compromises these natural antithrombotic protective mechanisms.[16,17] Lipids within the arterial wall, especially the oxidative products, also stimulate coagulation.

Another major factor that induces thrombogenicity of the arterial wall is the binding of active thrombin to arterial wall matrix; this matrix-bound thrombin activates platelets, converts fibrinogen to fibrin, may activate additional thrombin generation, and is relatively protected from inhibition by heparin.[18]

Specific receptor inhibitors to substances that activate platelets have shown the important in vivo role of thrombin in arterial thrombosis. Inhibition of thromboxane A_2, serotonin, or both did not significantly reduce ^{111}In-labeled platelet deposition or mural thrombosis after deep arterial injury by balloon dilatation in the pig. However, these receptor inhibitors did reduce acute vasoconstriction.[19] Subsequently, we found a dose-dependent inverse correlation of heparin dosage and plasma levels with quantitative ^{111}In-platelet deposition and ^{125}I-fibrinogen deposition and the incidence of mural thrombosis after deep arterial injury by balloon angioplasty in a prospective study of 6 different heparin dosages in the pig.[20] The use of low molecular weight heparin at 4 different dosages showed that the antithrombin was more important than the anti-Xa effect of heparin.[21]

Specific antithrombin therapy with hirudin inhibits platelet aggregation to thrombin but not to thromboxane A_2, adenosine diphosphate, serotonin, or collagen. Hirudin in a dosage that prolongs the activated partial thromboplastin time (APTT) to 2–3 times control totally eliminates mural thrombus and reduces platelet deposition to a single layer or less after deep arterial injury.[22] This documents the critical and primary role of thrombin in the mechanisms of arterial thrombosis. A slightly lower dosage of hirudin that prolongs the APTT to 1.7 times control prolongs the bleeding time to a similar degree as heparin, prolongs the thrombin time to greater than 6 times control, and reduces ^{125}I-fibrinogen deposition, but does not significantly reduce mural thrombosis or quantitative ^{111}In-platelet deposition. Thus the anticoagulant, antifibrin, antiplatelet, and thus antithrombotic effects occur at different dosages, which makes appropriate dosing critically important for therapeutic effect.

Five times the level of thrombin inhibition is required to inhibit platelet thrombi in pulmonary arteries compared with fibrin thrombi during disseminated intravascular coagulation without arterial injury.[23] Approximately 10 times greater thrombin inhibition is required to block thrombosis totally after deep arterial injury, compared with thrombosis after mild injury in association with a high-grade stenosis or during venous stasis.[22–24] Thus, larger amounts of thrombin are associated with deep arterial injury and require greater levels of thrombin inhibition to prevent arterial thrombosis. The greater blood levels of hirudin required to prevent arterial thrombosis totally after deep injury are compatible with the increased thrombin content of this pathologic state. We have recently demonstrated this with positive immunohistochemical staining for thrombin in mural thrombus overlying arterial segments with deep (type III) but not mild (type II) arterial injury.

Thrombin generation is greatly accelerated by an activator complex (prothrombinase complex), which is formed by the assembly of activated factors Va and Xa bound with calcium to a lipid membrane such as the platelet or other cellular membranes. Thrombin generation is increased 278,000 times by this activator complex.[25,26] Thrombin activation of factor V to Va enhances thrombin's own generation via the prothrombinase complex. Thrombin also activates factor XIII to XIIIa for cross-linking of fibrin and stabilization of thrombus following conversion of fibrinogen to fibrin.

Systemic factors: In addition to arterial wall substrates, systemic factors may also increase arterial thrombosis. Epinephrine infusion may enhance platelet deposition 3-fold.[27] Cholesterol feeding has also enhanced quantitative platelet deposition even after mild injury.[28] Lipoprotein(a) is homologous with the structure of plasminogen, decreases endogenous thrombolysis, and thus enhances thrombus formation during the continuous dynamic process of thrombosis and thrombolysis.[29] Lipoprotein(a) probably enhances thrombosis both as a circulating lipoprotein and as an arterial wall substrate in the extracellular matrix associated with fibrinogen within cells.[30] Platelets contain large amounts of plasminogen activator inhibitor type-1, which also may enhance thrombus formation, as suggested by the great resistance to endogenous and exogenous thrombolysis by platelet-rich arterial thrombi.[31,32] In addition, lipoprotein-associated coagulation inhibitor, which inhibits the interaction of tissue factor with factor VIIa, also may play a significant role in reducing arterial thrombosis. Lipoprotein-associated coagulation inhibitor is bound primarily to high-density lipoprotein cholesterol in the plasma, is also present in a free form, and is enhanced in its action by heparin.[33]

Rheology of blood flow: The rheology of blood flow is also important in arterial thrombosis. Small arteries with large flow velocities are at greater risk of thrombosis because platelet deposition increases directly with the shear force. Shear force is the difference in fluid or cell velocity at the center of arterial flow compared with the periphery. It is inversely related to the third power of the lumen diameter and indirectly to the flow velocity.[34] At high shear force, erythrocytes push platelets to the periphery, adenosine diphosphate is increased on cell surfaces, and platelet deposition is increased.[34–36] After type III or deep arterial injury, platelet deposition increases even more rapidly on the firmly anchored arterial thrombus. In the presence of type II or mild injury, platelet deposition only transiently increases, aggregates are readily washed away, and platelet deposition remains at a low and limited level. In an arterial stenosis, the concentration of platelets is greatest within the minimal lumen diameter. Distal to the stenosis in the region of relative stasis, a more fibrin-rich or reddish thrombus usually forms.[37] Thus, angioscopy of arteries from patients with unstable angina shows a whitish or platelet-rich thrombus when viewed antegradely[38] and a reddish or more fibrin-rich thrombus when viewed retrogradely via angioscopy during coronary bypass surgery.[39] Portions of a thrombus may intermittently embolize distally during growth of the thrombus, but a very rapid regrowth with accelerated thrombosis nearly always occurs in the presence of deep injury and a high-grade stenosis.[6,7,37]

VASOCONSTRICTION AND ARTERIAL INJURY

Vasoconstriction is common after acute arterial injury. After acute arterial injury by balloon dilatation in pigs, vasoconstriction occurs proximally and distally to the dilated region. In the dilated region, necrosis of smooth muscle cells is evident 24 hours after injury.[10,40,41] This vasoconstriction may be significantly reduced by aspirin, nitroglycerin, thromboxane receptor inhibition, or serotonin receptor inhibition.[19,40,41] The severity of vasoconstriction is directly related to the log of the platelet deposition. The reduction in platelet deposition with aspirin also reduced (but did not eliminate) vasoconstriction. Thrombin generation may also increase vasoconstriction, perhaps via its known ability to release endothelin.[42]

After angioplasty in humans, the acute vasoconstriction peaks at approximately 30 minutes after the procedure and thus may be missed unless specifically observed by delayed angiography. This

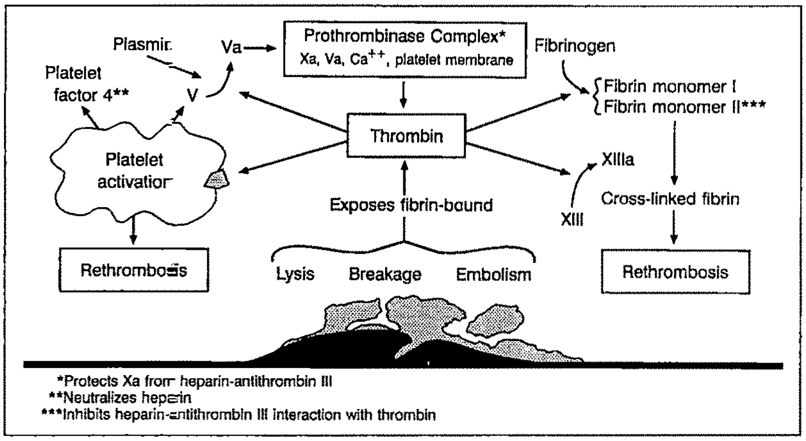

FIGURE 1. The central role of thrombin in rethrombosis is illustrated. Mechanisms of the marked thrombogenicity of mural thrombus and the difficulty of heparin completely blocking this process are depicted. Endogenous or exogenous lysis, spontaneous embolization, or mechanical dislodgement of thrombus exposes thrombin bound to fibrin. Thrombin activates platelets, activates factor V to Va (which leads to generation of more thrombin via the prothrombinase complex), converts fibrinogen to fibrin I and fibrin II monomers, and activates factor XIII to XIIIa (which cross-links fibrin). These processes combine to produce rethrombosis. Heparin may only partially prevent rethrombosis because *factor Xa within the prothrombinase complex is protected from heparin–antithrombin III inhibition, **platelet factor 4 secreted from platelets neutralizes heparin, and ***fibrin II monomer inhibits the action of heparin–antithrombin III. (Reprinted with permission from Webster et al.[59])

vasoconstriction is also preventable by an intravenous infusion of nitroglycerin but not necessarily by the routine use of calcium antagonists.[43] Thus intravenous nitroglycerin appears to be beneficial after coronary angioplasty.[43]

Vasoconstriction may be localized only to regions of endothelial injury, as shown by gentle denudation of endothelium in porcine coronary arteries, where vasoconstriction occurred only in the mildly injured region, but not in the distal uninjured region, when acetylcholine was infused at increasing steady-state dosages.[44] Regrowth of endothelium appears to be protective against acetylcholine-induced vasoconstriction in porcine coronary arteries, where endothelial-like cells are regrown after one week.[10,45] Hypercholesterolemia induced by cholesterol feeding induces type I injury (nondenuding endothelial dysfunction), which is associated with acetylcholine-induced vasoconstriction in porcine coronary arteries.[46]

Vasoconstriction increases the shear force and thus may increase platelet deposition and arterial thrombosis. The reduction in vasoconstriction with infusion of nitroglycerin may indirectly reduce thrombosis by reducing shear forces, but may also have a direct effect on reducing platelet deposition as observed experimentally and as suggested by the inhibition of platelet aggregation by the infusion of nitroglycerin in humans.[41,47]

MURAL THROMBUS

Mural thrombus is more thrombogenic than deeply injured arterial wall at either high or low shear and in the absence or the presence of a severe stenosis[48] Current antithrombotic therapy reduces recurrent ischemia in patients with unstable angina but does not eliminate the problem, which still remains in 15–40% of patients despite treatment with aspirin, heparin, or both.[49,50]

Residual mural thrombus with or without associated vasoconstriction probably explains most of the recurrent ischemic episodes in patients who present with unstable angina. The difficult problem of totally inhibiting growth of mural thrombus is centered on thrombin inhibition and is summarized in Figure 1. Thrombin adsorbed to fibrin remains active within residual thrombus. Endogenous or exogenous thrombolysis, mechanical breakage of thrombus, and spontaneous embolization all may expose active thrombin bound to fibrin. This thrombin may further activate platelets, activates its own generation by activating factor V to Va (enhances the development of the prothrombinase complex which increases thrombin generation by 278,000 times),[26] converts fibrinogen to fibrin, and further cross-links fibrin by activating factor XIII to XIIIa. In addition, inhibition of thrombin bound within the thrombus is relatively resistant to heparin because platelet factor 4 secreted from platelets inhibits the action of heparin, and fibrin monomer II inhibits the action of heparin–antithrombin III.[51,52] Specific thrombin inhibitors do not have these natural inhibitors and have greater access to thrombin within the thrombus because of their smaller molecular size.[25,51,53] Thrombin bound to fibrin requires 30–50 times the dose of heparin for partial inhibition (70–75% inhibition of generation of fibrinopeptide A) compared with inhibition of unbound thrombin in plasma.[53–54] The smaller molecules of specific thrombin inhibitors gain better access to thrombin bound to fibrin within the thrombus and thus completely inhibit thrombin (100% inhibition of fibrinopeptide A generation) whether it is bound within the thrombus or free within the plasma at the same dosage of inhibitor.[52,54]

Heparin is beneficial to patients with unstable angina[49,50,55–57] even though it does not completely inhibit thrombin within a thrombus or totally block growth of a mural thrombus.[20,53,54,58] Three retrospective studies in patients with unstable angina showed that heparin administration for 3–7 days prior to angioplasty improved the success of angioplasty, significantly reduced the incidence of total occlusion after angioplasty, and reduced the incidence of emergency bypass surgery, myocardial infarction, and death after the procedure.[55–57]

CURRENT RECOMMENDATIONS

Unstable angina is a high-risk thromboembolic event.[60] Thus maximal antithrombotic therapy is required and appears best achieved with combined anticoagulation and low-dose aspirin even though no trial has tested combined therapy against single therapy. The recent trial with combined therapy was designed to test differences from placebo, not between therapies.[49]

Currently we recommend intravenous heparin (100 U/kg bolus plus infusion to prolong the APTT to 2–3 times control) plus platelet inhibition with aspirin (160 mg loading dose and 80 mg/day thereafter). Heparin should be administered for at least 3–4 days prior to any coronary angiography in order to decrease the complications of a percutaneous transluminal coronary angioplasty (PTCA) procedure should it be deemed necessary.[55–57,61] Thus more prolonged anticoagulation appears to encourage endogenous lysis of residual mural thrombus.[61] In patients treated medically, heparin should be switched to warfarin (prothrombin time 1.5–1.8 times control, International Normalized Ratio [INR] 3.0–4.5) and continued for approximately 3 months along with aspirin at 80 mg/day for maximal antithrombotic therapy. Nitrates and calcium antagonists (especially diltiazem at 90 mg 4 times/day, which has been shown to reduce reinfarction in patients with non-Q-wave myocardial infarction, and unstable angina)[62] may also be combined in order to prevent coronary vasoconstriction or spasm associated with acute arterial injury. The reduction in vasoconstriction will decrease shear forces and may help reduce platelet deposition and mural thrombosis.

Patients with unstable angina may be treated medically without routine urgent coronary angiography if antithrombotic therapy is effective. A predischarge exercise test may be done in patients with no recurrent ischemia on medical therapy to discern signs of residual ischemia. If there is no ischemia at a low work load, patients may be continued on medical antithrombotic therapy and appropriate vasodilators to encourage endogenous lysis of any residual mural thrombus. Effective antithrombotic therapy may decrease the need for revascularization procedures in the future. Currently 40–50% of patients with unstable angina undergo revascularization procedures with either PTCA or coronary artery bypass graft surgery.

There does not appear to be a good rationale for thrombolytic therapy in patients with unstable angina because the emergency salvage of myocardium is not an issue in unstable angina; there is a very small but finite risk of intracerebral bleeding (0.3–0.6%) with systemic thrombolysis; and thrombolytic therapy administered for 24 hours or less has not been shown to improve the minimal lumen diameter or decrease morbidity significantly.[63] Newer antithrombotic therapies, which may totally block new formation of thrombus, are expected to increase endogenous thrombolysis. This should maximally clear luminal obstruction and may decrease the need for coronary revascularization in up to 50% of patients. This estimate is based on the fact that more than half of patients who present with acute coronary syndromes have a pre-existing minor lesion (<50% stenosis) by coronary angiography.[64–69]

The antithrombotic therapy that appears to be most promising for the future is inhibition of thrombin by a specific thrombin inhibitor. Hirudin can totally block thrombus growth and totally prevent new thrombus formation.[20,22] Other possibilities that have lower binding affinities to thrombin include argatroban (a synthetic thrombin inhibitor) or hirulog, a smaller fragment of hirudin.[54,70] Inhibition of thrombin generation proximal to its formation may be possible by inhibiting tissue factor or factors Xa, VIIa, or IXa, or by cleavage and destruction of factors Va and VIIIa by the infusion of activated protein C; inhibition of linking between platelets by preventing binding of fibrinogen, von Willebrand factor, or both with platelet glycoprotein membrane receptor inhibitors (such as glycoprotein IIb/IIIa) and inhibiting adhesion of platelets to the collagen receptor (glycoprotein Ia) or to von Willebrand factor (glycoprotein Ib and glycoprotein IIb/IIIa) may be possible.[71,72] A disadvantage of receptor inhibitors to glycoprotein IIb/IIIa of the platelet membrane receptor is ineffectiveness when used alone in situations of high thrombogenicity such as deep arterial injury; heparin must be used with it in these situations in order to prevent mural thrombus.[73–77] In addition, this receptor inhibitor is not effective at low shear rates.[73–77] Specific thrombin inhibition with hirudin appears most promising because it can totally prevent mural thrombosis and limit platelet deposition to a single layer after deep arterial injury and also is effective at high and low shear rates.[20,22,73,74]

The duration of therapy required to maximize endogenous lysis is unknown in animal and human studies. In addition, the human dosage of specific thrombin inhibitors requires careful study because there is a difference between the anticoagulant dosage, the antithrombotic dosage, the antifibrin dosage, and the antiplatelet dosages of these inhibitors.[22] Lower dosages of hirudin inhibit fibrinogen/fibrin deposition (APTT 1.7 times control) but higher levels are required (APTT 2–3 times control) to inhibit macroscopic mural thrombus and limit platelet deposition to a single layer.[22] Before large-scale clinical trials are carried out or this therapy is combined with a thrombolytic agent, the proper dosages in humans and the proper duration of therapy for prevention of thrombus and for completion of endogenous lysis and the prevention of return of thrombus need to be determined.

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Pathophysiology of Acute Coronary Syndromes

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The natural history of coronary artery disease is punctuated by clinical manifestations of unstable angina, acute myocardial infarction, and ischemic sudden death. These acute coronary syndromes share common pathophysiologic mechanisms that include fissuring of a plaque followed by varying degrees of dynamic coronary obstruction, which is due to vasoconstriction and coronary thrombosis. The response to plaque fissure is likely to be modulated by local and/or systemic procoagulant and anticoagulant–fibrinolytic activities. The key role of coronary thrombosis in acute coronary syndromes has substantial implications for prevention and treatment of complications of coronary atherosclerosis.

(Am J Cardiol 1991;68:16C–23C)

In the past few years, intensive investigations have focused on the pathophysiologic events leading to conversion of stable manifestations of atherosclerotic coronary artery disease (CAD) to its more acute and sinister manifestations: unstable angina, acute myocardial infarction (MI), and ischemic sudden death (acute coronary syndromes). Unstable angina, characterized by recurrent episodes of prolonged myocardial ischemia triggered predominantly by episodic reductions in coronary blood flow, is an important model for understanding the basic pathophysiologic events that lead to all acute ischemic syndromes. Acute coronary syndromes are the first clinical expression of CAD in about 30% of patients with CAD.

CORONARY ATHEROSCLEROTIC PLAQUE IN UNSTABLE ANGINA

The traditional angiographic indices of the severity of CAD (number of vessels with significant stenosis, percent diameter stenosis, minimal diameter, length of stenosis, and the presence or absence of collaterals) cannot accurately differentiate patients with stable CAD from those with unstable angina (Figure 1).[1–4] A detailed examination of the morphology of coronary stenosis in culprit arteries, using antemortem as well as postmortem angiography, shows that in at least 70–80% of patients with unstable angina, the stenosis is eccentric, with overhanging or irregular margins and intraluminal haziness or radiolucent filling defects—features rarely observed in the coronary arteries of patients with stable angina.[4,5]

Meticulous and detailed postmortem examination of atherosclerotic plaques in the culprit coronary arteries of unstable angina patients shows them to be complex, with fissures or cracks in the fibrous cap of the plaque (Figure 2). These fissures or ruptures usually occur either at the margins of the plaque in the area where the eccentric plaque-bearing segment joins the non-plaque-bearing segment of the arterial wall or in the center of the plaque.[6] Fissures average about 300–400 μm in length and vary in width from narrow slits to large gaps or ulcerations of the plaque surface.[7] Areas of hemorrhage are commonly observed and may be

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secondary to plaque fissure.[7] Coronary angioscopy has confirmed the presence of complex and fissured plaques in the culprit coronary arteries of patients with unstable angina undergoing coronary artery bypass surgery (Figure 3).[8]

POTENTIAL MECHANISMS OF PLAQUE FISSURE

The precise events leading to plaque fissure remain unclear. Fissures occur more frequently in plaques that are rich in extracellular and eccentric pools of lipid. However, they are not unique to severely occlusive atherosclerotic plaques, but also frequently occur in mildly occlusive plaques.[9–11] Pathologic studies show that often the plaque fissure develops at the margin of the atheroma, where the atheroma joins the normal arterial wall and plaque-fissure shows a predilection for thin acellular, lipid-rich, soft, or highly vascularized atheromatous plaques.[6,7,9]

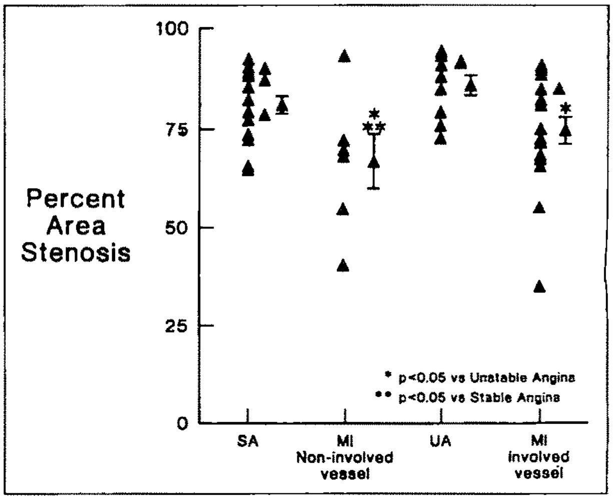

Figure 1. Comparative severity of coronary stenosis in the coronary arteries of patients with stable angina (SA), unstable angina (UA), and acute myocardial infarction (MI) following thrombolysis. Note the overlap in the severity of stenosis in the arteries of patients with SA and those of the culprit arteries of patients with UA and acute MI. (Adapted from *Circulation*.[3])

Richardson et al[6] demonstrated by means of in vitro computer models of arteries, that circumferential stress is greatest at the endothelial surface of the arterial wall, stress is concentrated at the junction of the fibrous cap with the more compliant normal arterial wall, and softer plaques tend to develop a higher shear stress.[12] These findings suggest that hemodynamic or mechanical stress associated with heartbeat bending and twisting of an artery, or increases in blood pressure (exercise, diurnal changes, sudden change in coronary tone) may contribute to fissuring of certain types of vulnerable plaque.[13] Experimental studies in mammalian atherosclerotic arteries show that a sudden surge of blood pressure in synergy with endothelial damage can produce plaque fissures.[7] Fissures may also occur when activated, subintimal, lipid-laden macrophages and other inflammatory cells release humoral mediators, such as proteases and tumor necrosis factor, which erode the plaque from within.[13,14]

Cinematographic studies of cleared human hearts and microsphere studies show that extensive neovascularization of atherosclerotic plaques is associated with a fivefold increase in medial flow compared to normal arterial wall with blood flow directed from adventitia towards the intima.[15,16] This increased vascularity of the atherosclerotic plaque from proliferation of vasa vasora may play a role in plaque fissure by providing a source of bleeding into the plaque and/or by bringing cellular and/or humoral mediators into the plaque, which may contribute to fissuring.[15,16] This point of view, however, has been challenged by Constan-

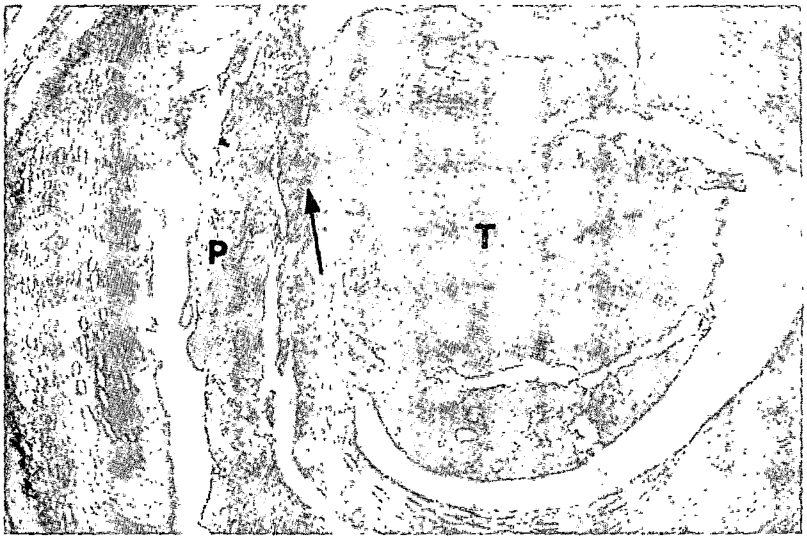

Figure 2. Histopathology of a coronary arterial stenosis showing an atherosclerotic plaque (P) with a fissure (arrow). An intramural and intraluminal thrombus (T) is attached at the site of the plaque fissure. (Adapted from Davies MJ, ed. Color Atlas of Cardiovascular Pathology. Oxford University Press, 1987.)

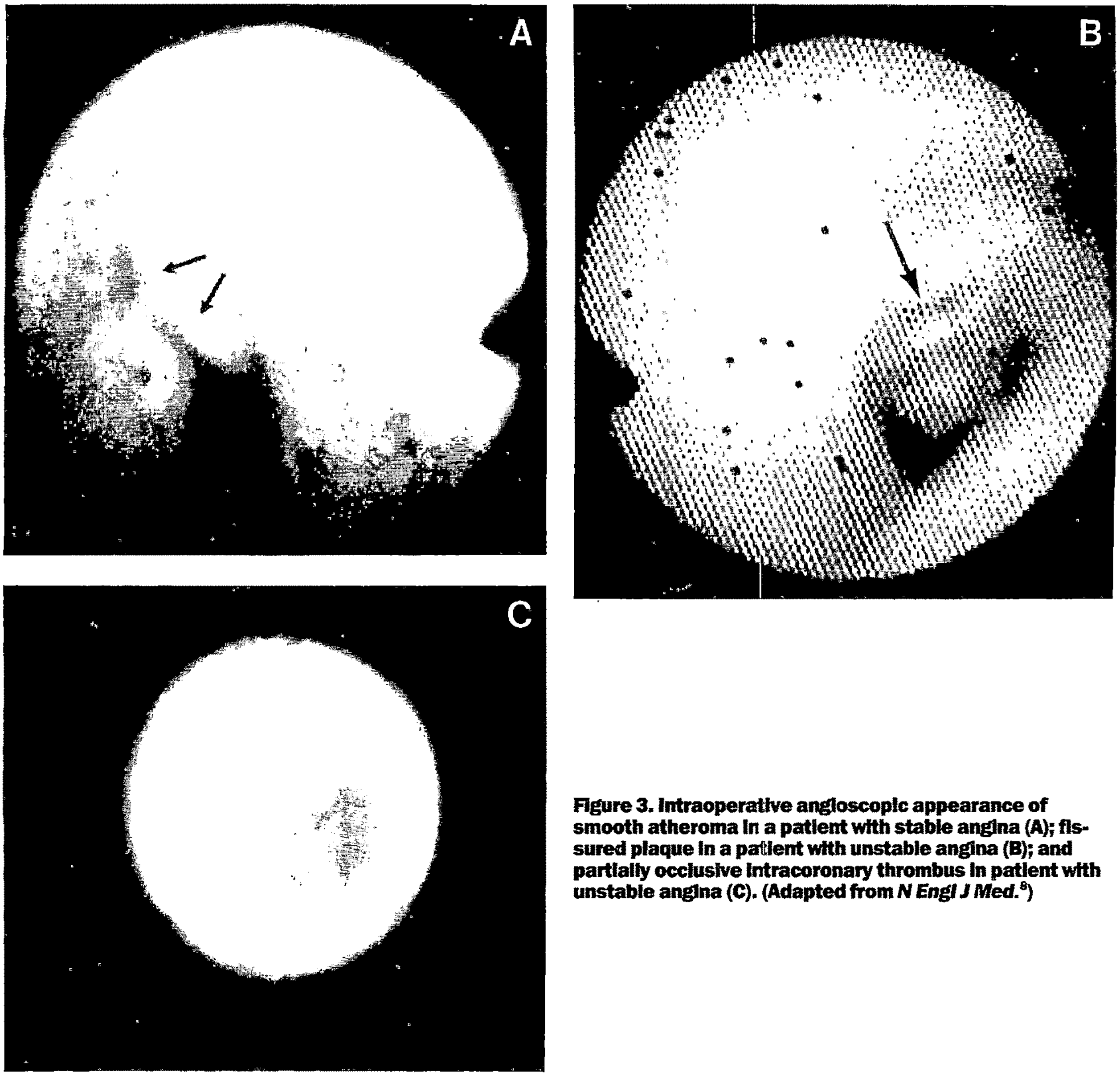

Figure 3. Intraoperative angioscopic appearance of smooth atheroma in a patient with stable angina (A); fissured plaque in a patient with unstable angina (B); and partially occlusive intracoronary thrombus in patient with unstable angina (C). (Adapted from *N Engl J Med.*[8])

tinides on the basis of pathologic findings.[17] Several recent studies suggest that plaques considered noncritical or angiographically insignificant (<50% diameter stenosis) may become the sites of subsequent plaque fissures with superimposed coronary thrombosis.[9–11,13,19]

Although the precise causes of plaque fissure remain unclear, a variety of factors may render a plaque vulnerable to rupture by damaging the endothelial lining or weakening the fibrous cap or the smooth muscle cells that produce the collagen for the fibrous cap. These factors include chemical or metabolic insults such as prolonged hyperlipidemia, high angiotensin levels, elevated acetoacetic acid levels (i.e., diabetes), nicotine, circulating immune complexes, inflammatory cells and their humoral products, and increased fragility of collagen from increased cross-linking or contraction.[17]

CONSEQUENCES OF PLAQUE FISSURE

Plaque fissure may abruptly change the geometry of a coronary stenosis, leading to a sudden increase in coronary luminal obstruction. In addition and perhaps more importantly, plaque fissure may trigger more dynamic mechanisms of coronary obstruction (i.e., abnormal vasomotor tone, platelet aggregation, and platelet–fibrin thrombus formation) (Table I). These dynamic factors are implicated in the intermittent coronary artery occlusion that leads to episodic coronary flow reduction and precipitation of unstable angina.

TABLE I Pathophysiology of Unstable Angina*

1. Fixed Coronary Stenosis
    - Fissured plaque
    - and
2. Dynamic coronary obstruction
    - Vasoconstriction
    - Platelet aggregation
    - Platelet–fibrin thrombus

*The interaction is between 1 and 2.

DYNAMIC FACTORS CONTRIBUTING TO EPISODIC CORONARY ARTERY OBSTRUCTION IN UNSTABLE ANGINA

Abnormal vasomotion: Atherosclerotic arteries have an exaggerated response to certain vasoconstrictor stimuli or a paradoxical vasoconstrictor response to stimuli that dilate normal blood vessels (Figure 4).[20–27] These abnormal or anomalous vasomotor responses of atherosclerotic arteries have been observed in experimental models, human arteries studied in vitro as well as in vivo, and resemble those of normal arterial strips from which endothelial lining has been deliberately removed.[28,29] Thus, atherosclerosis appears to impair the normal vasodilator effects of the endothelium.[22,30]

In normal endothelium, vasodilation appears to be mediated through the release of substances such as endothelium-derived relaxation factor (EDRF), which may be either nitric oxide or a nitrosothiol compound synthesized by the endothelium from arginine.[29,31] Stimuli that produce vasodilation in the presence of normal endothelium include acetylcholine, histamine, bradykinin, serotonin, substance P, adenosine diphosphate (ADP), adenosine triphosphate (ATP), calcium ionophore A23187, platelet-activating factor, thrombin, platelets, increased shear stress, increased blood flow, and exercise (endothelium-dependent vasodilators).[32,33] When the endothelium is damaged, such as occurs in atherosclerosis or hypercholesterolemia, the vasomotor response to endothelium-dependent vasodilators is blunted or converted to vasoconstriction. A recent study shows that endothelial cells in culture produce a potent vasoconstrictor peptide labeled endothelin.[34] Thus, endothelium may modulate vascular tone by releasing both vasodilator and vasoconstrictor substances. The hyperreactivity of the vascular smooth muscle cell may reflect atherosclerotic-induced endothelial dysfunction leading to deficient release of EDRF and/or excessive release of endothelin. It is still unclear whether an intrinsic abnormality of the vascular smooth muscle cell also plays a role.

Plaque fissure may contribute to vasomotor hyperreactivity by triggering platelet or leukocyte activation and platelet- or leukocyte-mediated vasoconstriction.[35] Furthermore, endothelial dysfunction with local thrombin formation may contribute to vasoconstriction. Even normal changes in vasomotor tone may significantly reduce blood flow in a severely stenotic coronary artery. Clinical observations that endothelium-independent vasodilators such as nitrates and calcium antagonists reduce the number of ischemic episodes in unstable angina patients suggest some role for coronary vasomotion in the pathogenesis of ischemia in unstable angina. However, the limited effect of these agents in reducing the risk of acute MI argues that mechanisms other than vasoconstriction are more important.

Platelet aggregation: In experimental models of partial coronary artery stenosis and endothelial injury, Folts et al[36] initially reported that spontaneous intermittent coronary occlusion and cyclical variations in coronary blood flow distal to the stenosis result from intermittent platelet aggregation. These cyclical flow variations are abolished or reduced by agents that inhibit platelet aggregation and/or inhibit the effects of platelet-derived thromboxane and serotonin, such as aspirin, thromboxane synthetase inhibitors, thromboxane and serotonin receptor antagonists, and certain α-adrenergic antagonists. Cyclical variations are exaggerated by platelet aggregatory agents such as ADP, platelet-activating factor, α agonists, nicotine, thrombin, and exercise (Figure 5).[37–45]

Evidence of platelet activation in humans with unstable angina includes elevated circulating and/or urinary levels of products of platelet activation

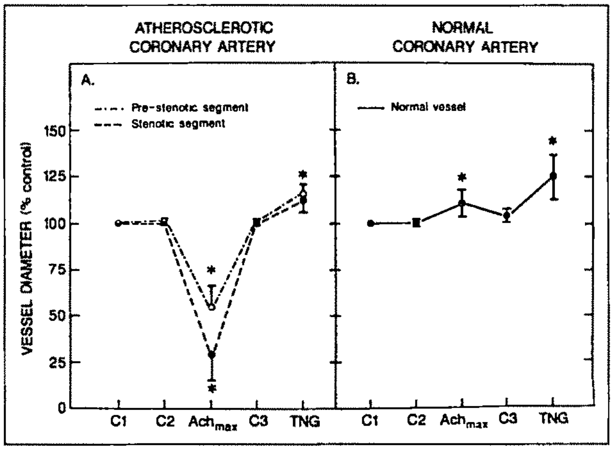

Figure 4. Vasomotor response of the atherosclerotic and normal coronary arteries to acetylcholine. Note that atherosclerotic segments react with a transient decrease in luminal diameter, whereas the normal arteries react with a slight increase in luminal diameter. C=control; Ach=acetylcholine; TNG=nitroglycerin. (Adapted from *N Engl J Med.*[21])

such as β-thromboglobulin, platelet factor IV, and thromboxane metabolites[46–48]; pathologic evidence of platelet microemboli in myocardial microvasculature downstream from the culprit coronary stenosis[49]; and finally, a strong protective effect of aspirin against development of MI in patients with unstable angina.[50–52] Careful autopsy studies by Falk[49] show that platelet microemboli are seen in about 50% of patients who die soon after the onset of ischemic symptoms.[53] These emboli are almost exclusively seen in arterioles and in small arteries downstream from the artery with a fissured plaque and may be associated with scattered foci of myocardial necrosis. Platelet aggregates on a fissured plaque may reduce coronary blood flow by direct occlusion or through the release of humoral mediators such as serotonin and/or thromboxane. In the absence of normal endothelial function, these mediators produce vasoconstriction. In addition, platelet emboli may produce ischemia or infarction and, conceivably, trigger fatal disturbances of rhythm and conduction.

Coronary thrombosis: Intraluminal coronary thrombosis appears to play an important role in the pathogenesis of unstable angina. Angiographic studies show intraluminal filling defects and lucencies, indicating a thrombus at the site of a complex coronary stenosis in 1% to 85% of patients with unstable angina.[54–61] The inconsistencies in the reported angiographic incidence of intracoronary thrombus may be related to several factors, including variability in the timing of angiography in relation to the symptoms and less than optimal sensitivity of the angiographic criteria for the detection of thrombus.

A relatively low incidence of thrombus has been reported in studies where angiography was performed several days to weeks after the last episode of angina.[54,55,57–59] In contrast, a higher incidence (50–85%) has been reported when angiography was performed soon after the last episode of unstable angina.[56,60,61] Gotoh et al[61] observed evidence of intracoronary thrombus in 57% of patients with unstable angina when angiography was

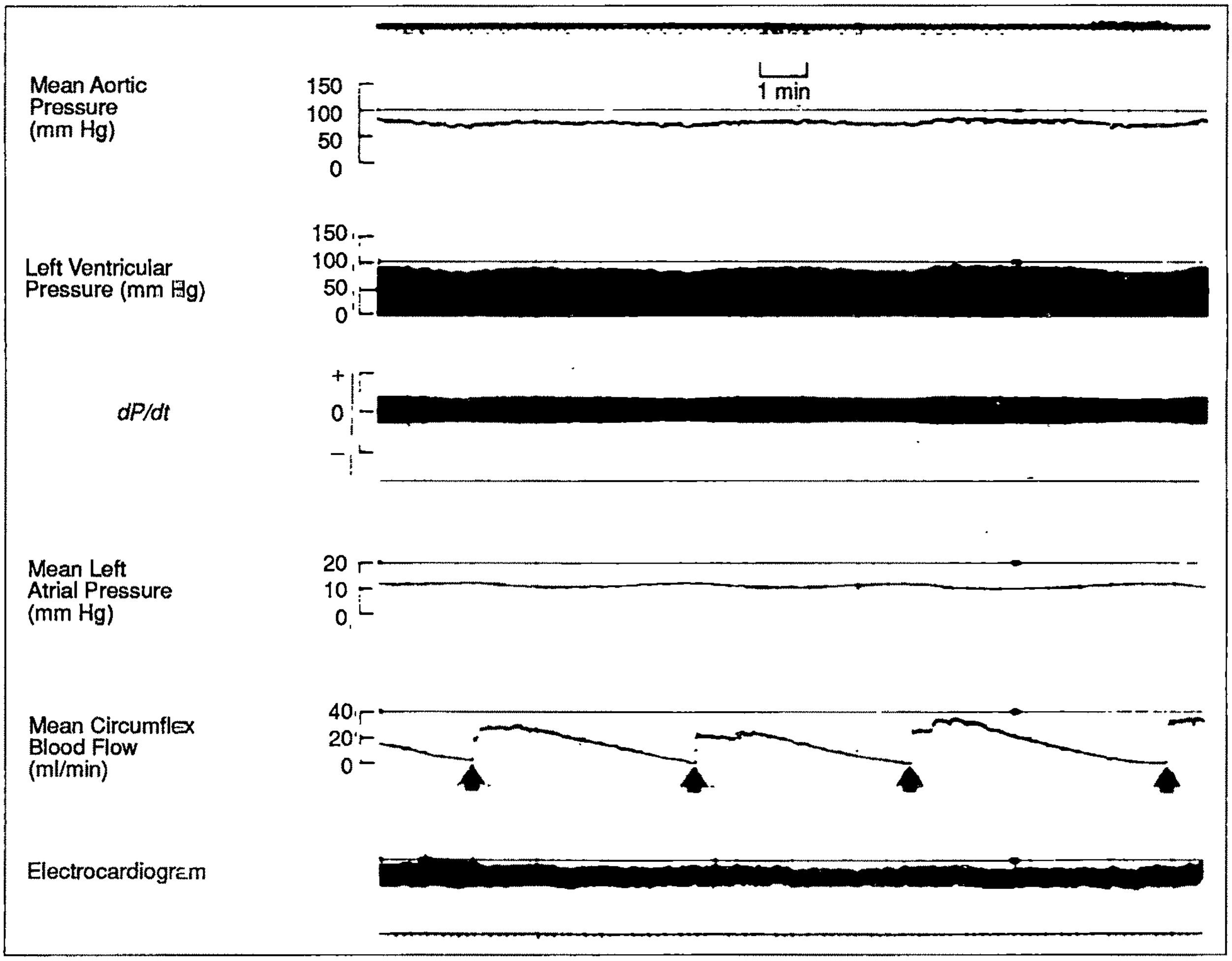

Figure 5. Platelet-mediated spontaneous cyclical coronary flow variation in the canine coronary stenosis model. (Adapted from *J Am Coll Cardiol.*) 1984;6: 1417.

performed during episodes of ischemia. Their study used both morphologic features and response to intracoronary thrombolytic therapy as the criteria for thrombus. More importantly, they documented the dynamic and evanescent nature of the intracoronary thrombus in unstable angina. Intraoperative angioscopic observations also show a high prevalence of visible intraluminal thrombus in the culprit arteries of patients with unstable angina undergoing bypass surgery (Figure 3).[8]

The presence of ongoing thrombosis in unstable angina is further supported by indirect evidence, such as elevated levels of circulating fibrin and urinary markers of thrombin-mediated fibrin formation, such as fibrinopeptide A and other fibrin-related antigens.[62] Histopathologic studies confirm the high prevalence of intraluminal and intraintimal thrombus at the site of a fissured atherosclerotic plaque in patients with unstable angina and other acute coronary syndromes.[7,9,10,49,63,64] The frequent development of acute MI, a complication that is now considered to be the consequence of prolonged coronary artery occlusion due to an intraluminal thrombus, is further evidence of the important pathophysiologic role of intracoronary thrombus in unstable angina. Finally, the beneficial effects of anticoagulants (and in some cases thrombolytic therapy) in reducing ischemia and the frequency of infarction argue strongly that coronary thrombosis plays an important role in unstable angina.[52,65]

FACTORS CONTRIBUTING TO PLATELET AGGREGATION AND CORONARY THROMBOSIS IN UNSTABLE ANGINA

Plaque fissure appears to be the initial event that creates a milieu for platelet adhesion, aggregation, and subsequent fibrin–platelet thrombus formation. After fissuring occurs, the contents of the plaque are exposed to circulating platelets. They in turn adhere to the exposed fibrillar collagen (type I) and elastin matrix of the plaque through the interaction of von Willebrand factor and adhesive glycoprotein platelet receptors (Ib and possibly Ia).

The high shear rate in the vicinity of a severe coronary stenosis contributes to platelet adhesion and aggregation by a cyclooxygenase independent mechanism. Deep arterial wall injury is associated with a more intense and prolonged platelet deposition against the arterial wall at high as well as low shear rates. This is in contrast to more superficial endothelial injury where platelet deposition is higher at high shear rates, with maximum deposition occurring within 10–20 minutes and dislodgement of platelets caused by the blood flow.[66] The model of superficial injury and high shear rate simulates a coronary stenosis with mild ulceration of the plaque; the deep injury model simulates an area of arterial stenosis with a deep plaque fissure.[13] Following platelet adhesion, exposure of another type of platelet glycoprotein receptor (IIB/IIIA), binding fibrinogen, von Willebrand factor, and possibly fibronectin bridge activated platelets, leading to platelet aggregation. Platelet-derived procoagulants, as well as the procoagulant effect of the "tissue factor" expressed by the plaque and released from the plaque, activate the clotting cascade, leading to thrombin formation. Thrombin in turn leads to fibrin formation, further platelet aggregation contributing to fibrin–platelet thrombus formation, and vasoconstriction.

ROLE OF HYPERCOAGULABILITY

In addition to the severity of the plaque fissure, the intensity and the duration of the thrombotic response may be further modulated by the balance between systemic or local procoagulant and fibrinolytic state as well as the aggregability of platelets. Hypercoagulable states associated with elevated fibrinogen levels, increased triglyceride and lipoprotein(a) levels, chronic smoking, elevated factor VII activity levels, and depressed fibrinolytic state due to high levels of plasminogen activator inhibitor type 1 may particularly predispose certain individuals to thrombosis, whereas an efficient fibrinolytic system and a hypocoagulable state may protect others from thrombotic consequences of plaque fissure.

Autopsy studies in patients who die from the complications of unstable angina frequently show that coronary thrombi of varying ages are seen at the site of a fissured plaque, suggesting ongoing waves of thrombosis and its dynamic nature in the acute coronary syndromes.[49] Incorporation and organization of thrombi into the plaque may contribute to accelerated progression of CAD. This has been angiographically demonstrated in up to 70% of patients with unstable angina who were serially studied during progression from a stable to an unstable state.[11,67]

A UNIFYING MECHANISM TO EXPLAIN THE PATHOPHYSIOLOGY OF ACUTE CORONARY SYNDROMES

The acute coronary syndromes of unstable angina, acute MI, and ischemic sudden death appear to share a common pathophysiologic basis, with plaque fissure in the coronary artery as the patho-

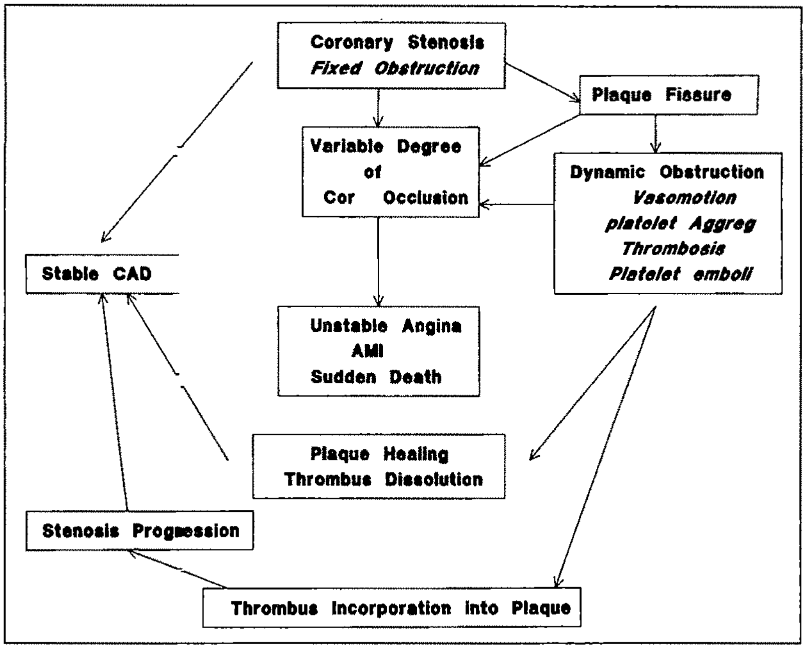

Figure 6. A conceptual model of the pathophysiology of acute coronary syndromes of unstable angina, acute myocardial infarction (AMI), and sudden cardiac death. CAD=coronary artery disease.

logic hallmark (Figure 6).[9,10] In addition to the plaque fissure varying amounts of intraluminal and intramural platelet–fibrin thrombus constitute the acute intimal lesion observed in the vast majority of patients who die of acute coronary syndromes.[9,10] When plaque fissure is associated with brief periods of coronary occlusion (due to platelet aggregation, vasoconstriction, or evanescent platelet–fibrin thrombosis), the result is unstable angina; when the coronary occlusion is more prolonged, the result is acute MI. Subendocardial infarction is more likely to develop when spontaneous reperfusion occurs, before occlusion-induced necrosis has spread transmurally, or when the transmural spread of necrosis from a permanent coronary occlusion is halted by well-developed epicardial collaterals. Sudden cardiac death is likely to occur when a large area of myocardium is rendered ischemic, leading to a fatal disturbance in cardiac rhythm or conduction. This may develop during brief or prolonged periods of coronary occlusion or perhaps when platelet aggregates embolize downstream from the acute coronary lesion.

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Growth Factors in Pathogenesis of Coronary Arterial Restenosis

Bojan Cercek, MD, Behrooz Sharifi, PhD, Peter Barath, MD, PhD, Lee Bailey, MD, and James S. Forrester, MD

Restenosis occurs in 25% to 55% of patients within 6 months of successful angioplasty. The major histologic component of the restenotic lesion is intimal hyperplasia, which is almost certainly driven by growth factors. After vascular injury, smooth muscle cells proliferate, reaching a maximum rate at day 2. Smooth muscle cell proliferation diminishes as the vessel surface is re-endothelialized at about day 7, and by week 4 the smooth muscle cell mitotic rate returns to baseline of <1% per day. The events of the histologic evolution of arterial injury can be used to create a hypothetical paradigm for the role of growth factors in restenosis. Restenosis might logically be prevented by an inhibitory intervention at any of the various steps in the healing process.

(Am J Cardiol 1991;68:24C–33C)

Within 6 months of successful angioplasty, restenosis occurs in 25% to 55% of patients.[1,2] Autopsy and atherectomy studies have identified intimal hyperplasia as the major histologic component of the restenotic lesion.[3–5] Insights from these studies have prompted several investigators to begin identification of the cells and the cell products responsible for restenosis. This discussion will first describe the histologic appearance of intimal hyperplasia as it evolves following vascular injury, and why this evolution is almost certainly driven by growth factors. This will be followed by a discussion of the most important growth factors and their known actions, and finally by speculation on the possible individual functions of growth factors in the genesis of intimal hyperplasia and, by inference, in the process of restenosis.

HISTOPATHOLOGY OF RESTENOSIS

The histopathology of restenotic lesions was first established by autopsy studies in patients who died several months after angioplasty,[6] and later in tissue removed by atherectomy from living patients.[5] The histologic appearance is independent of both the type and the location of vascular injury.[7] Thus, balloon inflation, atherectomy, lasers, and even Gore-Tex grafts produce the same response, in both peripheral and coronary arteries.[8] The restenotic lesion consists of proliferating mesenchymal cells in a loose connective tissue matrix of sparse collagen fibrils and acid mucopolysaccharides (Figure 1). The mesenchymal cells, which are large and stellate, appear to be smooth muscle cells that have modulated from the quiescent contractile phenotype to the more primitive, metabolically active synthetic phenotype. The abundant extracellular matrix surrounding these phenotypically modified cells often has an abundance of new capillaries, indicating concomitant endothelial cell proliferation. This histologic pattern is termed intimal hyperplasia.[9]

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EXPERIMENTAL MODELS OF INTIMAL HYPERPLASIA

The factors responsible for smooth muscle cell proliferation and extracellular matrix secretion are now being defined using in vitro and in vivo experimental models. The most widely studied model of vascular injury is that induced by balloon inflation in rats[10–12] or rabbits.[13] This form of injury closely approximates that in humans, since there is both endothelial denudation and damage to the media.[14] After injury, smooth muscle cells proliferate first in the media. About 30–40% of the medial smooth muscle cells proliferate, reaching a maximum at 2 days. These cells begin to migrate to the intima at about 4 days. In the intima, smooth muscle cell proliferation is maximal 7 days after denudation. As the vessel surface is re-endothelialized at about 7 days, smooth muscle cell proliferation begins to diminish (Figures 2 and 3). By 4 weeks the smooth muscle cell mitotic rate in the media returns to the baseline rate of <1%/day.[15] In permanently denuded areas, on the other hand, intimal smooth muscle cell proliferation can persist at levels of 4% for as much as 12 weeks af injury.[10]

Since growth factors regulate proliferation endothelial cells, migration and proliferation smooth muscle cells, and extracellular matrix seci tion throughout the body, they may influence tl progression of intimal hyperplasia through the action on the cell cycle. Cells in the adult arteri wall are normally quiescent.[15] Such cells are said be in phase G_0 of the cell cycle. When stimulated l extracellular factors, the cell enters the G_1 phase, state of activation that precedes the S phase, whe the DNA content of the cell is duplicated mitosis. In tissue, therefore, the amount of prolife ation depends predominantly on the relative fra tion of cells in the G_1, compared with the G_0, phas Growth factors stimulate progression from the C to G_1 phase and hence cell proliferation.[16]

The G_1 phase is subdivided into a phase i which the cell becomes competent to proliferate after which it is stimulated to progress to the phase. During progression, there is protein synthe sis, in contrast to the competence phase. In th

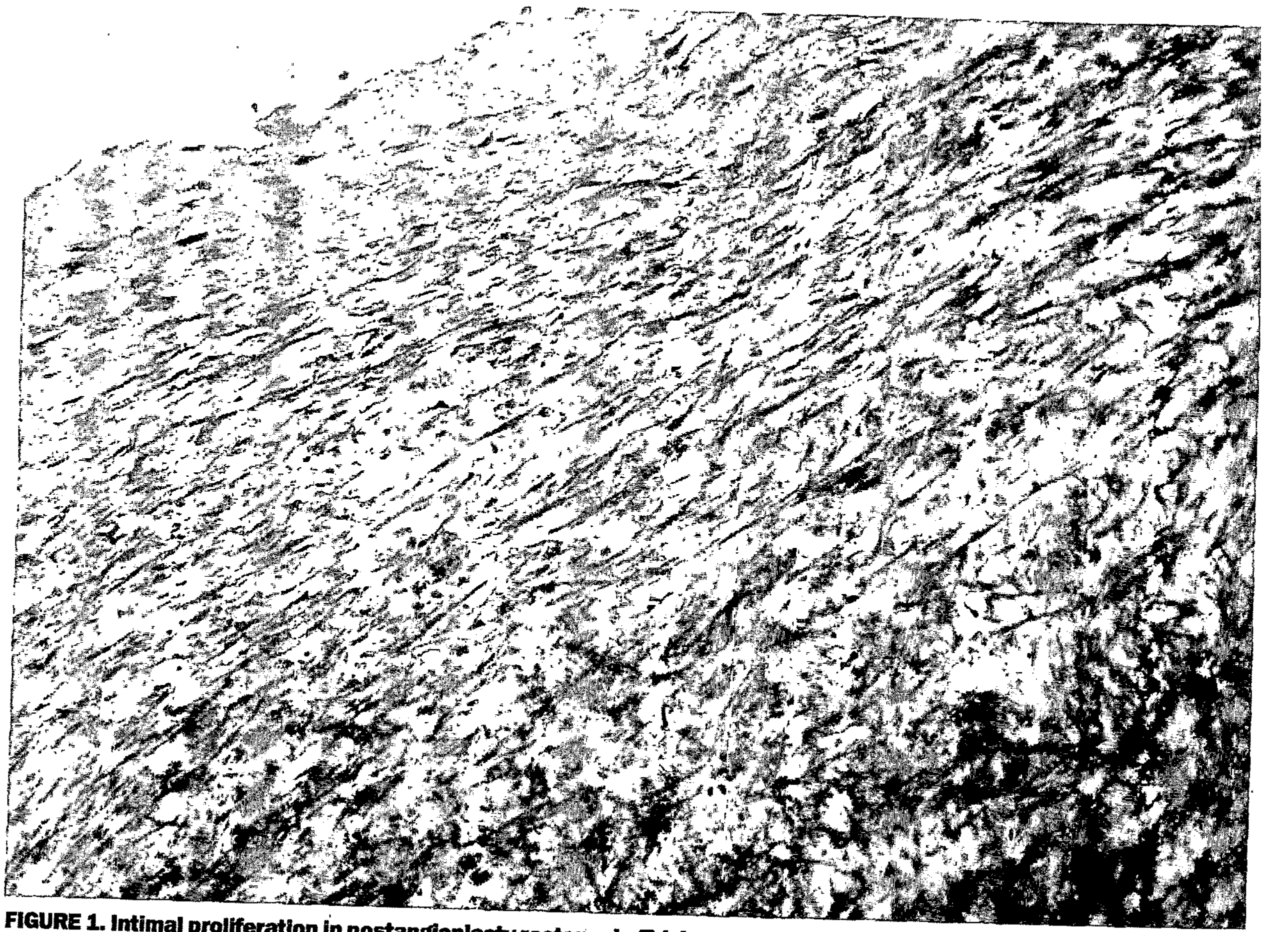

FIGURE 1. Intimal proliferation in postangioplasty restenosis (Trichrome stain). Smooth muscle cells with cytoplasmic projections and abundant extracellular matrix. (Courtesy of Dr. M. Fishbein.)

final step prior to entry into the S phase, enzymes are organized into a complex to catalyze DNA synthesis. Growth factors are classified as competence or progression factors. Smooth muscle cells become competent after exposure to platelet-derived growth factor. Those competent cells will progress to the S phase if provided with a progression factor. For smooth muscle cells, insulin-like growth factor type 1 (IGF-1) is a progression factor.[16]

Our current knowledge of the effects of growth factors in controlled systems like cell culture is quite extensive. Growth factors are expressed by many different cell types, often act on the same cells that express them, and may have inhibitory or proliferative effects, depending on the environment. We have much less knowledge about interactions between growth factors and about their effects in tissues in vivo. Thus, our analysis of the role of growth factors in restenosis must be somewhat speculative, since it mostly involves selection of data derived from experimental conditions that are not necessarily identical to vascular injury in man.[17]

PLATELET-DERIVED GROWTH FACTOR, THROMBOSPONDIN, AND INSULIN-LIKE GROWTH FACTOR TYPE-1

Three important mediators of smooth muscle cell proliferation: The initiating event in intimal hyperplasia is platelet adherence and degranulation. Platelet adherence to the injured area occurs immediately, peaks at about 1 hour, and is greatly diminished within 24 hours.[13] Platelets release growth factors and other biologically active proteins. The best-characterized growth factor released by platelets is platelet-derived growth factor (PDGF).[18]

The name "platelet-derived growth factor" is somewhat misleading. Although PDGF was originally discovered as a product released by platelets, various PDGF isoforms are also produced by many other normal and transformed cells.[19] Structurally, PDGF is composed of two polypeptide chains, denoted A and B. The A chain is encoded by the PDGF A-chain gene[20] and the B-chain by c-*sis*, the proto-oncogene of the simian sarcoma virus transforming gene, v-*sis*.[21] Both homodimers (AA and BB) and a heterodimer (AB) have been identified.

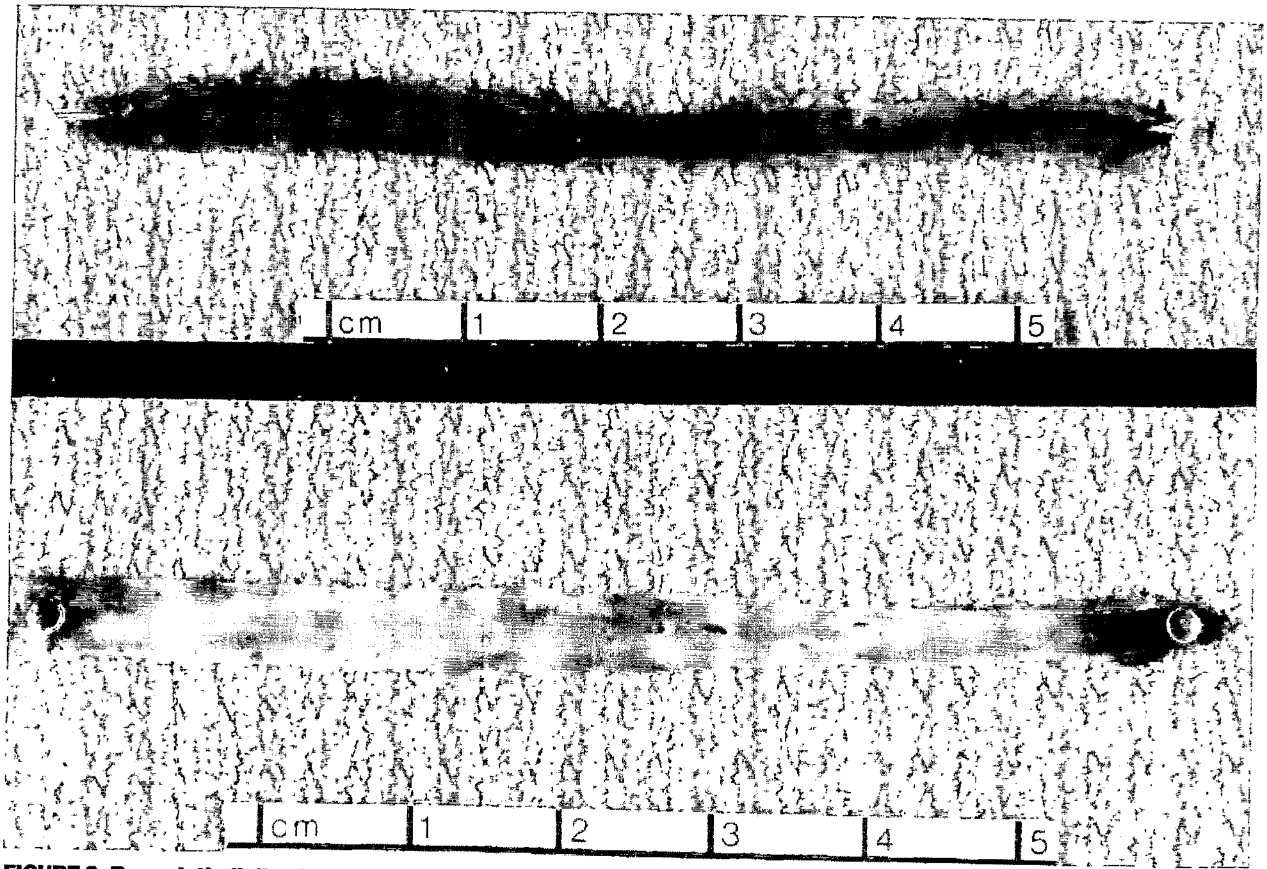

FIGURE 2. Re-endothelialization of rat aorta after balloon denudation. *Upper panel:* 3 days after denudation, thoracic aorta is still de-endothelialized and stained blue with Evans Blue dye. *Lower panel:* 14 days after denudation, re-endothelialization of thoracic aorta is almost complete.

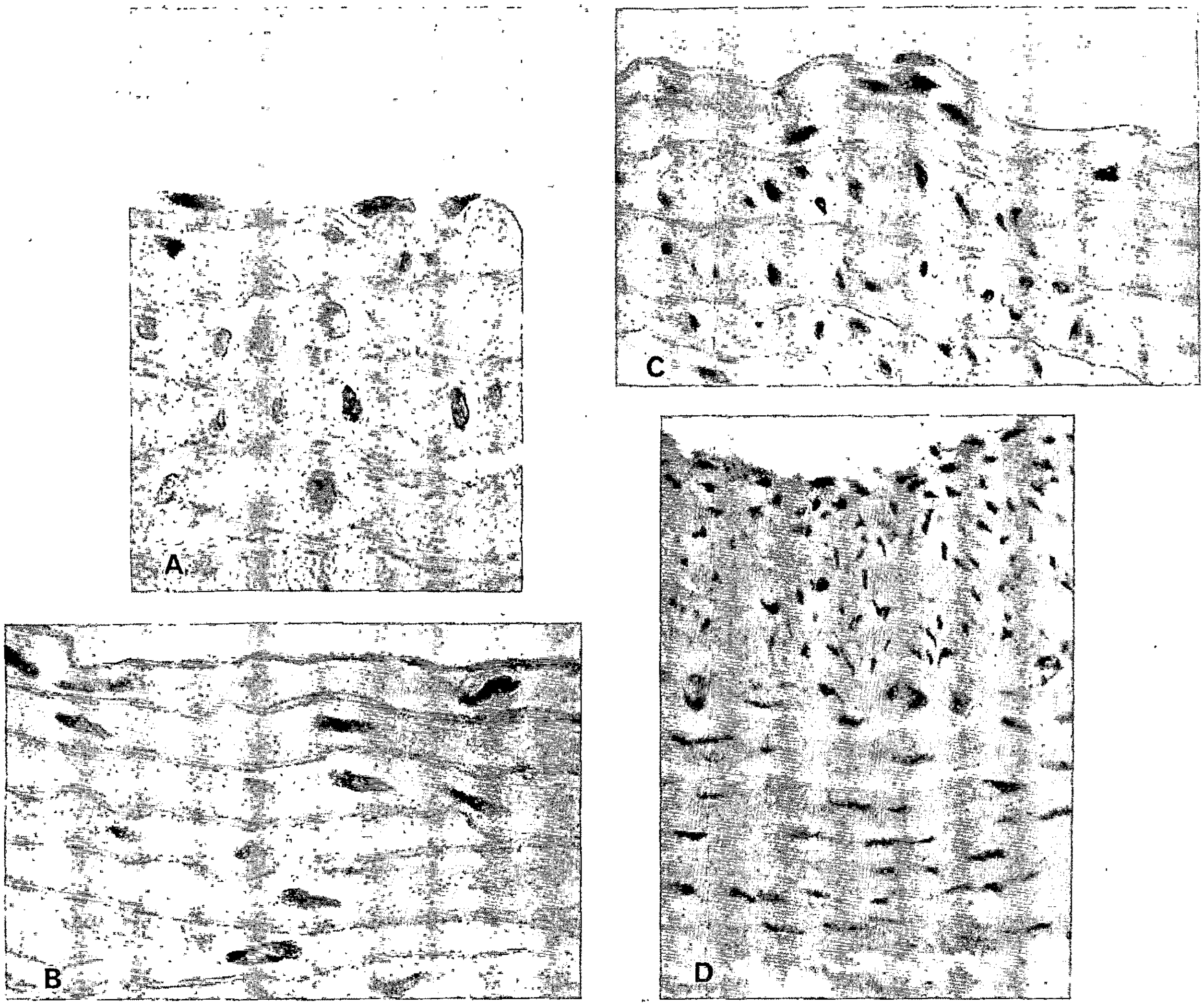

FIGURE 3. Histologic sections of control and rat aortas after balloon denudation (hematoxylin and eosin stain). *A*: Zone of normal aorta in control rat. *B,C*: Zone of denudation in rat aorta 1 and 3 days after denudation. *D*: Zone of denudation in rat aorta with neointimal proliferation at 14 days after denudation.

Beyond the platelet source, PDGF-like factors are produced by vascular endothelial cells[22] and vascular smooth muscle cells.[23] Smooth muscle cells from injured arteries express both PDGF A-chain and B-chain genes.[24,25] The production of different isoforms differs both by cell form and experimental conditions. In human serum, only 7% of the PDGF is the BB isomer, whereas that secreted by human endothelial cells contains twice that amount of PDGF-BB.[26] These differences probably have biologic importance. For instance, PDGF-AA has low mitogenic activity and no effect on chemotaxis of human fibroblasts but is a potent mitogen in 3T3 cells, whereas PDGF-AB is a potent stimulator of human fibroblasts.[27]

The analysis of the production and possible functions of PDGF is complicated not only by the existence of three isoforms but also by the differences in multiple forms of specific cell membrane receptors.[28] Two distinct PDGF receptor genes have been identified, denoted α and β.[29,30] The α receptor subunit binds A and B chains, whereas the β receptor subunit binds only B chain with high affinity (Figure 4).[31] This difference in receptor subunit affinity for the three isoforms suggests that the effects of PDGF isoforms are regulated by both the availability of the ligand and by the receptor subunit on the target cell.[32]

The evidence implicating PDGF as a central factor in wound healing comes from several sources. Addition of PDGF increases the collagen formation in wound chambers[33] and the width of the newly synthesized dermal tissue layers in skin wounds.[34] In vascular injury, there is also substantial evidence for a role of PDGF. In animals with limited endothelial damage, infusion of PDGF-BB stimulates smooth muscle cell proliferation.[35] Thrombocytopenia suppresses smooth muscle cell

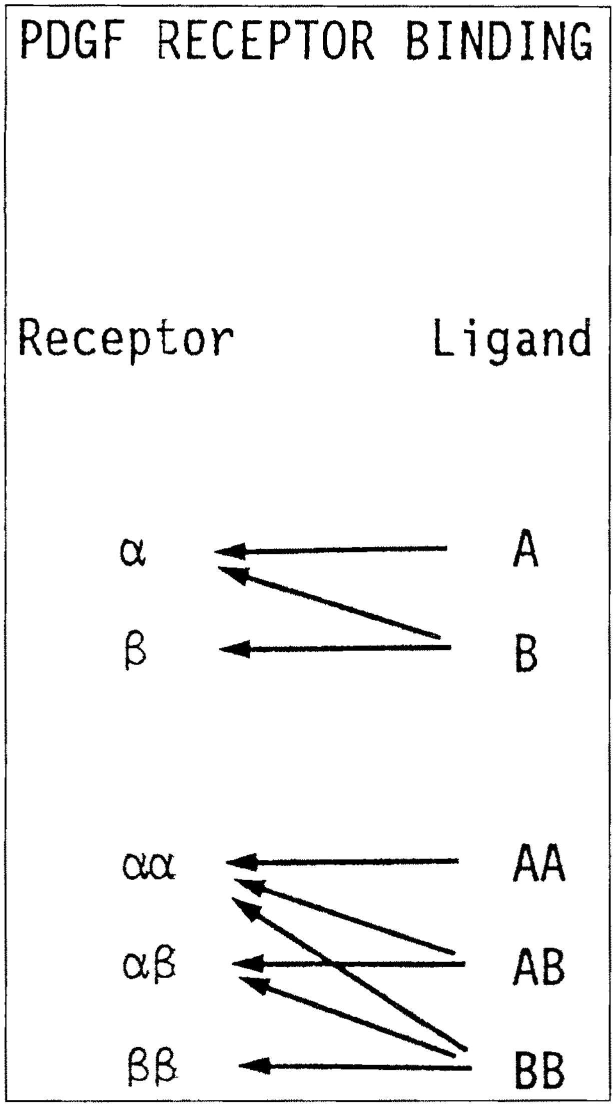

FIGURE 4. Platelet-derived growth factor (PDGF) receptor α subunit can bind PDGF A and B chains; subunit β can bind only PDGF B chains. Homodimer PDGF AA can bind only to αα receptor, PDGF AB can bind to αα and αβ receptors, and PDGF BB can bind to all three PDGF receptor classes. (Adapted from *Proc Natl Acad Sci USA.*[31])

migration to the intima, but does not alter medial smooth muscle cell proliferation.[36] Thus, PDGFs may be primarily responsible for providing a stimulus to smooth muscle cell migration, whereas growth factors that originate from other cellular sources may be required for smooth muscle cell proliferation. Finally, in human atherosclerotic arteries[37] and explanted saphenous vein grafts,[38] PDGF-A chain mRNA has been detected by in situ hybridization, suggesting a role in the smooth muscle cell proliferation that characterizes atheroma formation.

Stimulation of smooth muscle cell proliferation by PDGF, however, clearly involves its interaction with several other factors, most notably thrombospondin[39] and IGF-1.[40] In vascular smooth muscle cells, PDGF induces both thrombospondin[41] and IGF-1 mRNA expression.[42] Both thrombospondin and IGF-1 appear to be essential for smooth muscle cell proliferation, since monoclonal antibodies to either protein inhibit smooth muscle cell growth.[43,44] Additionally, the inhibitory effect of heparin on smooth muscle cell growth may be through prevention of thrombospondin binding.[45]

Perhaps the most important growth factor to interact with PDGF is IGF-1. IGF-1 is a progression factor for PDGF, indicating that it is required for PDGF to exert its full mitogenic effect in cultured smooth muscle cells.[40] IGF-1 alone is a poor stimulator of growth, yet smooth muscle cells stimulated by PDGF do not progress readily to the S phase unless IGF-1 is also present.[46] In vivo studies also show synergism between the two growth factors. When IGF-1 was added in topical therapy of experimental full thickness epidermal wounds, epidermal growth increased 2-fold and the number of connective tissue cells and hydroxyproline content increased 3-fold, with a concomitant increase in the organization and maturation of collagen fibers.[47]

Changes in IGF-1 gene expression at the site of vascular injury are striking. Our studies have shown that the IGF-1 mRNA is expressed in the normal smooth muscle cells of rat aorta and that local IGF-1 mRNA content increases 9-fold 1 week after experimental vascular injury (Figure 5).[48] By in situ hybridization, IGF-1 mRNA transcripts are predominantly localized to medial smooth muscle cells (Figure 6).[49] Thus, signals elicited by the injury stimulate local IGF-1 expression by smooth muscle cells. Although the biochemical inducer(s) of IGF-1 expression have not been identified, one reasonable candidate is PDGF. Our studies and those of others have also found that IGF-1 protein accumulation is maximal on the luminal surface.[50]

The expression of IGF-1 in the vessel wall is regulated by both systemic (endocrine) and local (paracrine) factors. After hypophysectomy to eliminate growth hormone, the principal endocrine regulator of IGF-1, basal aortic IGF-1 mRNA content is markedly reduced. The relative increase in IGF-1 mRNA after injury, however, is preserved even in the absence of growth hormone.[40] These data suggest that basal vascular IGF-1 expression is controlled by circulating growth hormone, whereas local induction of IGF-1 mRNA after injury is

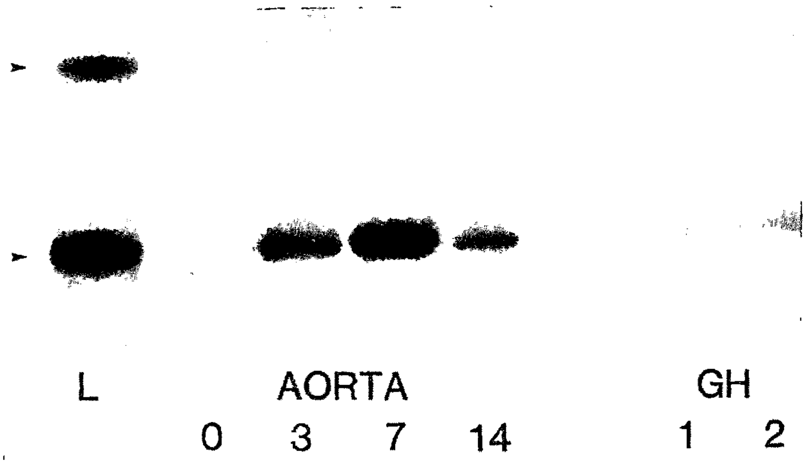

FIGURE 5. Regulation of alternative 5′ insulin-like growth factor type 1 (IGF-1) mRNA transcripts in the rat aorta after balloon denudation. Total RNA from liver (lane L), and aortas before (lane 0), 3 (lane 3), 7 (lane 7), and 14 (lane 14) days after denudation and from rats treated with growth hormone (lanes GH 1 and 2) were hydridized with an IGF-1 riboprobe complementary to class A IGF-1 mRNA. Arrows indicate protected fragments of 322 (class A) and 241 (class C) bases. (Reprinted with permission from American Heart Association and *Circulation Research*.[48])

controlled by paracrine factors. Consistent with this hypothesis, our studies have found that neointimal proliferation is decreased in hypophysectomized rats, but after supplementation with growth hormone returns to the same level as in nonhypophysectomized rats (unpublished observation).

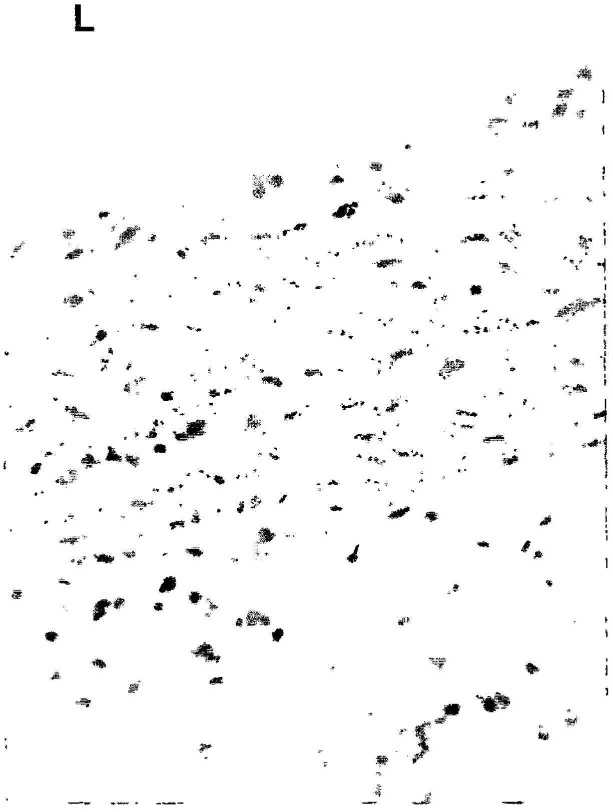

FIGURE 6. Localization of 5′ insulin-like growth factor type 1 (IGF-1) mRNA variants in rat aorta 14 days after balloon denudation by in situ hybridization. L=lumen.

FIBROBLAST GROWTH FACTORS, TRANSFORMING GROWTH FACTOR-ALPHA, AND EPIDERMAL GROWTH FACTOR

The interaction between endothelial and smooth muscle cells: The fibroblast growth factors (FGFs) belong to the group of polypeptide mitogens that share the property of heparin affinity and are now referred to as heparin-binding growth factors.[51,52] Class I heparin-binding growth factors are anionic, expressed in neural tissue kidneys and myocardium. Class II heparin-binding growth factors are cationic, have wide tissue distribution, and commonly characterized as basic FGF (bFGF).[53] Binding of FGF to heparin sulfate proteoglycan occurs in the basement membrane of the endothelial cell.[54,55] This association protects and stabilizes FGF in vivo.

The potential involvement of FGFs in the process of restenosis stems from the findings that cultured endothelial[56] and vascular smooth muscle cell[57] both express and respond to FGF and that FGFs are potent angiogenic factors.[58] Quiescent endothelial cells do not stain for the bFGF protein, whereas regenerating endothelial cells show abundant immunostaining with bFGF antibody.[59] Further, after arterial wall injury FGF stimulates endothelial[60] and smooth muscle cell proliferation.[61] After the gene for bFGF was cloned, observers found that several oncogenes have a 40–50% homology to this factor[62] and mammalian cells transfected with bFGF genes are partially transformed.[63] Finally, bFGF is a potent stimulus to its own expression[55]: This autocrine mechanism, similar to PDGF-B, may be an important mechanism for amplifying the rapid proliferation in response to injury.

There are both high-affinity and low-affinity receptors for FGF.[64] The low-affinity receptor for FGF, a heparin-like substance, may concentrate FGF on cell surfaces and facilitate its binding to the high-affinity receptors.[65] High affinity receptors for FGFs are expressed after crushing injury to the blood vessel.[66]

At least two additional closely related growth factors, transforming growth factor-α (TGF-α)[67] and epidermal growth factor,[68] probably play an important role in proliferative response after vascular injury. TGF-α has an approximately 30% structural similarity with epidermal growth factor,[69,70] and the 2 growth factors bind to the same receptor.[69,71] Although binding is equipotent in vitro, TGF-α has a more potent vascular action[72,73] and is a more potent angiogenic mediator in vivo.[74] TGF-α, like bFGF, induces its own expression.[73]

Our investigations show that TGF-α mRNA is not detectable in normal rat aorta, but it is expressed after balloon denudation and localized to smooth muscle cells.[75] The source of TGF-α immediately after injury may be either activated macrophages,[76] or an EGF-like peptide released by platelets.[77] It is secreted in a membrane-bound form[78] and may be modified by a neutrophil-secreted elastase to its mature form.[79] Thus, the process of inflammatory cell invasion of the wound site may be important both as a method for activating local growth factors as well as a primary source for their expression.

The interaction between endothelial and smooth muscle cells after injury is also unquestionably critical, because smooth muscle cell proliferation is greatest at the sites of least re-endothelialization.[12] Conversely, when the endothelial surface is restored, smooth muscle cell proliferation begins to diminish.[80] The mechanisms responsible for suppression of smooth muscle cell proliferation after re-endothelialization are undefined, but may involve heparin and transforming growth factor-β (TGF-β).

TRANSFORMING GROWTH FACTOR-BETA: MAJOR STIMULATOR OF EXTRACELLULAR MATRIX PRODUCTION

Transforming growth factor-β (TGF-β) is entirely unrelated to TGF-α in structure, biologic activity, and receptor binding.[81] The similarity in names relates only to the initial discovery that both are involved in cell transformation.[82,83] Several isoforms (denoted 1–5) have been identified. TGF-β is the most important factor regulating extracellular matrix production.[84] It stimulates production of proteoglycans, collagen, and fibronectin and regulates the receptors for these proteins.[85] In cultured smooth muscle cells, exposure to TGF-β increases collagen II mRNA and protein secretion severalfold.[86] Finally, TGF-β inhibits the action of proteolytic enzymes that destroy connective tissue.[85] This latter effect involves 2 distinct mechanisms: decrease in the secretion of proteases, and increase in the formation and secretion of protease inhibitors.[87,88] Thus, the combined actions of TGF-β serve to augment the accumulation of matrix proteins.

Although TGF-β is abundant in platelets,[89] both endothelial and smooth muscle cells also produce it and express its receptor.[90] The effect of TGF-β on cell proliferation is variable.[91] TGF-β stimulates proliferation in some connective tissue cells, whereas it is a potent inhibitor of proliferation in epithelial cells.[92] In cultured aortic smooth muscle cells, TGF-β inhibits growth in subconfluent monolayers, but stimulates growth in confluent cultures.[93] The bimodal effect of TGF-β on smooth muscle cell proliferation is regulated by stimulation of endogenous production of PDGF-AA at low concentration[94,95] and down-regulation of PDGF-α receptors at high concentrations.[95,96] Endothelial cells normally do not express PDGF receptors,[97] and endothelial regrowth is unimpeded in the presence of TGF-β in vivo.[59] The tissue concentration of TGF-β increases transiently in the arterial wall after injury, peaking prior to the phase of extracellular matrix production.[98]

GROWTH FACTORS AND PATHOGENESIS OF THE RESTENOSIS: A SYNTHESIS OF CURRENT KNOWLEDGE

The histologic evolution of arterial injury is well defined.[99,100] Immediately after injury, platelets accumulate at the site of injury. Within a few days, platelets have largely disappeared. At about 48 hours, smooth muscle cells in the media start to proliferate and then migrate to the injured area. Endothelial cells also begin to proliferate at the margin of the wound. At approximately 1 week, the endothelial surface is restored, and accumulation of extracellular matrix begins to become apparent.

These histologic events can be correlated with current knowledge about the injury response to create a hypothetical paradigm for the role of growth factors in restenosis. In the initial phase of the healing response, degranulation of adhering platelets releases PDGF, TGF-β, epidermal growth factor, and thrombospondin. The inflammatory cells that invade the wound site both secrete and release membrane growth factors. These mechanisms probably account for the rapid increase in IGF-1, TGF-α, and bFGF in local tissue concentration. Stimulated by PDGF, thrombospondin, and other growth factors, medial smooth muscle cells modulate to the synthetic phenotype. The change in phenotype is accompanied by autocrine secretion of growth factors that stimulate proliferation within about 48 hours of injury. At the same time bFGF, TGF-α, and epidermal growth factor stimulate endothelial cell proliferation. Endothelial cells are stimulated to initiate autocrine secretion of growth factors, including FGF and TGF-α. As the endothelial cell margins come together, at 1–2 weeks, TGF-β begins to inhibit endothelial cell proliferation. The accumulating TGF-β secreted from the smooth muscle and endothelial cells is also a potent inducer of extracellular matrix production. As the endothelial integrity is restored, extracellular matrix begins to accumulate in the subintima. Over the ensuing 3–6 months, extracellular matrix deposition creates the histologic appearance of smooth muscle cells embedded in a mass of extracellular matrix. Gradually, smooth muscle cells return to the quiescent contractile phenotype, and the extracellular matrix evolves to consist predominantly of collagen, producing the late appearance of a raised scar at the injury site. The prevention of restenosis, therefore, might logically occur by an inhibitory intervention at any one of these different steps in the healing process.

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Newer Concepts in the Treatment of Unstable Angina Pectoris

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Unstable angina patients should be hospitalized and treated with antianginal drugs to control their symptoms and with aspirin or heparin to reduce the risk of myocardial infarction. Heparin is probably preferable to aspirin acutely, because it also reduces the risk of refractory angina. However, aspirin therapy should be started before heparin is discontinued, to prevent the rebound in symptoms, and continued long-term. Unless specifically contraindicated, coronary arteriography should be performed to identify patients who might benefit from coronary bypass surgery or angioplasty. Control of risk factors is important for long-term outcome.

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Unstable angina is the most common diagnosis among patients admitted to coronary care units. Although the short-term mortality rate is less than 2%, approximately 10% of patients with this form of angina will develop myocardial infarction (MI) in the hospital. The goals of treatment for unstable angina are thus 3-fold: (1) to prevent angina and ischemic episodes; (2) to prevent MI; and (3) to control or eliminate risk factors to ameliorate long-term prognosis. Treatment related to the third goal is extremely important but will not be discussed further in this article because it is similar to that applied to other patients with coronary disease. Table I lists the commonly applied treatments for unstable angina that have definite effects on the prevention of angina and the prevention of MI. Evidence to support these conclusions will be presented in the following discussion.

ANTIANGINAL DRUGS IN THE TREATMENT OF UNSTABLE ANGINA

Beta-adrenergic blockers, calcium antagonists, and a variety of nitrate preparations including intravenous nitroglycerin are routinely used to treat patients with unstable angina. These drugs reduce the symptoms of stable angina and presumably have the same effect in unstable angina as well. However, it is difficult to prove this point based on data from clinical trials, for several reasons. Many studies are not parallel placebo-controlled or report only combined end points; others primarily include patients whose angina is probably caused by coronary spasm, and the trial results may not be applicable to a broader spectrum of patients with unstable angina. Gottlieb et al[1] reported that the addition of propranolol to baseline therapy of nifedipine and nitrates reduced both angina and electrocardiographic (ECG) evidence of ischemia to a significantly greater extent than placebo. In another study, the combination of propranolol and nitrates produced better angina relief than nifedipine in previously untreated patients.[2] In one uncontrolled study,[3] propranolol

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TABLE I Effect of Treatment in Unstable Angina

	Prevent Angina	Prevent Infarction
β-blockers	Yes	Unproven
Calcium antagonists	Yes	Unproven
Nitrates, intravenous nitroglycerin	Yes	Unproven
Aspirin	No	Yes
Heparin	Yes	Yes
Thrombolytic therapy	Unlikely	Unlikely
Bypass surgery	Yes	No
Coronary angioplasty	Yes	Unlikely

and diltiazem were equally effective in reducing angina, whereas another uncontrolled trial[4] showed similar results with intravenous nitroglycerin and a combination of oral and cutaneous nitrates.

The ability of these drugs to control symptoms of myocardial ischemia in unstable angina does not necessarily imply that they are also able to prevent MI. Table II lists the incidence of MI in unstable angina studies in which this information was reported separately and routine therapy did not include aspirin or heparin. The overall infarction rate (9.7%) does not appear to be lower with any of the drugs employed; differences between studies reflect differences in patient selection and the duration of follow-up. With an event rate of approximately 10%, the sample sizes of these studies of unstable angina are too small to detect a minor or modest effect of treatment on the infarction rate. Yusuf et al[6] provided an overview of patients in the β blocker trials with threatened infarction, i.e., prolonged ischemic pain without ECG evidence of infarction at entry. At least in this poorly characterized group, β blockers may indeed prevent infarction; infarctions developed in 29% of the β blocker patients and 32% of the control subjects—a 13% risk reduction ($p < 0.04$).

TABLE II Myocardial Infarction Rates in Unstable Angina Studies with Antianginal Drugs

Reference	Treatment Groups	Interval	MI Rate
Gottlieb et al[1]	Propranolol, nifedipine, nitrates	4 weeks	6/42 (14%)
	Placebo, nifedipine nitrates		3/39 (8%)
Muller et al[2]	Nifedipine	14 days	9/63 (14%)
	Nitrates, propranolol		9/63 (14%)
Théroux et al[3]	Propranolol, nitrates	1 month	2/50 (4%)
	Diltiazem, nitrates		3/50 (6%)
HINT[5]	Placebo		9/84 (11%)
	Nifedipine	48 hours	14/89 (16%)
	β-blocker		12/160 (8%)
	Nifedipine, β-blocker		13/182 (7%)
Total			80/822 (9.7%)

MI = myocardial infarction.

RATIONALE FOR ANTIPLATELET AND ANTITHROMBOTIC THERAPY

Angiographic,[7] angioscopic,[8] and pathologic[9,10] studies show that plaque rupture or fissuring, with formation of an acute occlusive or nonocclusive mural thrombus, is an important mechanism in the pathogenesis of the acute ischemic coronary syndromes such as unstable angina and MI. Exposure of the contents of the plaque results in a thrombogenic surface for interaction with platelets from the arterial blood. Platelets thus activated release vasoconstrictive substances such as serotonin and thromboxane A_2. In addition, adenosine diphosphate (ADP) is released, which may also contribute to recruitment and activation of neighboring platelets, ultimately leading to mural platelet-thrombus growth. Plaque rupture also results in the release of tissue thromboplastin and the activation of the coagulation system, which leads to thrombin generation. In addition to catalyzing the conversion of fibrinogen to fibrin, which stabilizes the platelet-rich thrombus, thrombin is also a potent platelet activator that may enhance the platelet-thrombus mass. Thus, these intracoronary thrombi have a large platelet and fibrin component.[11] Indeed, an increase in plasma thromboxane A_2 production (a marker of platelet activation)[12] and an increase in serum fibrinopeptide A formation (a marker of ongoing thrombin formation and thrombosis),[13] have been documented in unstable angina. In addition, vasoconstrictive substances released from activated platelets may further reduce luminal diameter at the site of thrombosis.[10]

Therefore, a rational approach is to use antithrombotic drugs to prevent or reduce the formation and propagation of such mural thrombi, and this technique has been employed as an antithrombotic approach to the management of unstable angina. The potential effectiveness of these drugs depends on their ability to interfere with several essential reactions associated with arterial thrombogenesis. Aspirin inhibits platelet function by irreversibly blocking the enzyme cyclooxygenase, an enzyme that converts arachidonic acid to prostaglandin endoperoxides, and ultimately to thromboxane A_2, a powerful vasoconstrictor and stimulant to platelet aggregation. Aspirin only partially inhibits platelet aggregation induced by ADP, collagen, or thrombin.

Heparin is a mixture of mucopolysaccharide chains of various lengths. It acts by forming a complex with antithrombin III, which then inhibits not only thrombin, but other serine proteases (factors XIIa, XIa, IXa, and Xa). In addition,

TABLE III Effect of Aspirin on the Combined Incidence of Death and Nonfatal Myocardial Infarction (MI) in Unstable Angina

Reference	No. of Patients	Time to Enrollment	Duration of Study	Death Nonfatal MI Placebo	Aspirin	Risk Reduction	p Value
Lewis et al[15]	1,266	<48 hr	12 wk	10.1%	5.0%	51%	0.0005
Cairns et al[16]	555	<8 days	18 mo	17.0%†	8.6%†	51%†	0.008†
Théroux et al[17]	239*	Mean 8 hr	6 ± 3 days	11.9%	3.3%	71%	0.012
RISC[18]	388*	Mean 33 hr	90 days	17.6%	7.4%	58%	0.0042

*Excluding heparin-treated patients.
†Results according to actual treatment (not intention to treat).

heparin affects hemostasis by virtue of its platelet inhibitory effect.[14] Heparin molecules differ in their antithrombin and anti-factor Xa activity; low molecular weight heparins, for example, have less antithrombin and more anti-factor Xa activity.

Aspirin: There is overwhelming evidence that aspirin prevents MI in patients with unstable angina. Each of 4 randomized, double-blind, placebo-controlled trials reported a significant risk reduction, ranging from 51% to 71% (Table III). Only men were enrolled in the study of Lewis et al.[15] Aspirin (324 mg per day) was begun within 48 hours of admission and patients were followed for 12 weeks. The study of Cairns et al[16] entered patients (both male and female) within 8 days of admission and followed them for a mean of 18 months. Aspirin (325 mg) was given 4 times daily. Despite these differences, both studies reported results that were strikingly similar.

In the study of Théroux et al,[17] patients were enrolled a mean of 8 hours after their last episode of chest pain, received aspirin (325 mg) twice daily, and were followed for 6±3 days, until definitive therapy was selected after coronary arteriography. This study design optimizes experimental conditions by eliminating any confounding effects from revascularization procedures and by reducing dropouts and noncompliance. The results reported extend the conclusions of previous studies: The beneficial effect of aspirin is operative in the acute, subacute, and chronic phases of unstable angina.

Low-dose aspirin (75 mg/day) was used in the study from Sweden (risk of myocardial infarction and death during treatment with low dose aspirin and intravenous heparin in men with unstable coronary artery disease [RISC Study][18]), and the treatment interval extended from a mean of 33 hours after admission to 90 days. Yet the results were similar—a 58% risk reduction, from 17.6% to 7.4%. Nearly half of the RISC patients had non-Q-wave infarction without unstable angina at study entry. The beneficial effect of aspirin on the primary end point (death plus nonfatal infarction) was observed for both unstable angina ($p=0.04$) and non-Q-wave infarction ($p<0.0001$).

In the Physicians' Health Study, a primary prevention trial, low-dose aspirin reduced the risk of MI by 44%.[19] In the Persantine-Aspirin Reinfarction II Study (PARIS), aspirin reduced the combined endpoint of coronary death plus nonfatal MI by 24% in survivors late after MI.[20] This drug also preserves patency of saphenous vein bypass grafts[21-23] and improves short-term survival with and without thrombolytic therapy after acute MI.[24] In addition, aspirin also prevents platelet aggregation and cyclic flow reductions in severely stenotic coronary arteries of dogs,[25] an experimental model analogous to unstable angina. The ability of aspirin to prevent infarction in unstable angina is therefore concordant with the effect of this drug in related coronary syndromes, and its beneficial effects are probably related to its antithrombotic properties. There is no convincing evidence, however, that aspirin prevents angina.

Heparin: Table IV summarizes the effect of heparin in the acute phase of unstable angina as assessed in 3 randomized, double-blind, placebo-controlled trials. Telford and Wilson[26] randomized 400 patients with "intermediate coronary syndrome," defined to include unstable angina and non-Q-wave infarction, into a double-blind, placebo-controlled, factorial design trial of heparin and atenolol. Almost half the patients (186) were later withdrawn because of incorrect recruitment. Atenolol had no effect on the incidence of MI. Only 3 of 100 heparin-treated patients, compared to 17 of 114 patients who were not receiving heparin, developed MI within the week of the study. The dose of heparin was 5,000 U intravenously every 6 hours.

Théroux et al[17] included only patients with unstable angina in their study, and heparin was administered as a continuous infusion, with the dose adjusted to maintain the coagulation time at 1.5–2 times control. Excluding the aspirin-treated patients, MI occurred in 1 of 118 heparin and 14 of

TABLE IV Effect of Heparin on the Combined Incidence of Death and Nonfatal Myocardial Infarction (MI) in Unstable Angina

Reference	Terms Used to Describe Patients	No. of Patients	Duration of Study	Death Nonfatal MI		Risk Reduction	p Value
				Placebo	Heparin		
Telford and Wilson[26]	Intermediate syndrome*	214	7 days	14.9%‡	3.0%	80%	0.024
Théroux et al[17]	Unstable angina	236†	6 ± 3 days	11.9%	0.8%	93%	<0.001
RISC[18]	Unstable CAD*	397†	5 days	6.0%	5.6%	7%	NS

*Unstable angina plus non-Q-wave infarction.
†Excluding aspirin-treated patients.
‡Includes atenolol-treated patients.
NS = difference not significant.

118 control patients, a risk reduction of 93%. Refractory angina, defined as recurrent bouts of angina with ischemic ECG changes or recurrent angina requiring urgent intervention, occurred in 27 control patients compared with only 10 in the heparin group (risk reduction 63%, p=0.002). A rebound effect often occurred when heparin was discontinued before aspirin was started.[27]

In contrast to these two trials, the RISC study did not show a statistically significant benefit from heparin.[18] Half of the RISC patients had non-Q-wave infarction and half had unstable angina. Heparin was given as an intravenous bolus of 5,000 U every 6 hours for 24 hours, with the dose reduced thereafter by 25%. When heparin was discontinued after 5 days, 12 of 199 controls and 11 of 198 heparin patients had died or developed MI. The lack of benefit from heparin in the RISC study as compared to the previous studies may be due not only to the difference in heparin administration, but also to the longer interval before the initiation of treatment in RISC or differences in the patients studied.

The results of a recent Italian trial[28] suggest that continuous, as opposed to intermittent, heparin administration is necessary to ensure efficacy in unstable angina, at least with respect to control of ischemic episodes. Unstable angina patients who were refractory to conventional antianginal therapy were randomized to heparin infusion, heparin bolus, or aspirin. Heparin infusion reduced angina attacks by 94% and silent ischemic episodes by 71% ($p < 0.001$ for both end points). Intermittent heparin reduced angina by only 30% and ischemic episodes by only 19%; the change with aspirin was even less. The response to heparin infusion was significantly ($p < 0.001$) better for both end points than the response to the other 2 treatments.

The pathophysiologic conditions in the culprit artery are probably quite similar in unstable angina and after successful thrombolytic therapy for MI. In the Heparin-Aspirin Reperfusion Trial,[29] the rate of infarct artery patency, 7–24 hours after initiation of recombinant tissue-type plasminogen activator (rt-PA), was higher with heparin than with aspirin, 82% versus 52% ($p < 0.0001$). Since heparin, when given with rt-PA, does not increase the early patency rate,[30] these findings suggest that heparin can prevent early reocclusion after successful thrombolysis. This benefit is analogous to the ability of heparin to prevent infarction in unstable angina.

Thrombolytic therapy: Thrombus formation undoubtedly plays an important role in the pathophysiology of unstable angina. Since thrombolytic therapy is safe and effective in acute MI, a condition caused by acute coronary occlusive thrombus formation, it is therefore not surprising that thrombolytic therapy has been tested with enthusiasm in unstable angina.

Thirteen studies of thrombolytic therapy for unstable angina are summarized in Table V. In 6 of them, no control group was included, and none of the studies included more than 100 patients. In most cases, quantitative measurements of lesions were obtained through computer-assisted techniques and coronary arteriography was not performed before or after treatment. In studies meeting these criteria,[35,40,42] the degree of improvement in culprit lesion severity was small and marked improvement was identified in only a minority of cases. For example, only 5 of 36 patients reported by Ambrose et al[35] showed angiographic improvement after intracoronary streptokinase; mean stenosis severity changed from 84% to 83%. An uncontrolled study reported improvement at 24 hours in 16 of 22 cases with total or subtotal occlusions.[38] Nicklas et al[40] reported an insignificant decrease in stenosis severity, from a mean of 71% to 63% after rt-PA therapy, and Williams et al[42] reported decreases of 3–5% with low-dose rt-PA, high-dose rt-PA, or placebo. In the latter study, all patients received concomitant aspirin and a constant heparin infusion; resolution occurred in most patients with visible intracoronary thrombus irrespective of thrombolytic therapy.

TABLE V Thrombolytic Therapy for Unstable Angina

Reference	Patients (agent/control)	Agent	Route	Angiographic Improvement	Clinical Improvement
Lawrence et al[31]	20/20	Streptokinase	Intravenous	No angiography	Yes
Rentrop et al[32]	5	Streptokinase	Intracoronary	No	No
Vetrovec et al[33]	12	Streptokinase	Intracoronary	Minor	Yes
Mandelkorn et al[34]*	17	Streptokinase	Intracoronary	Yes	—
Ambrose et al[35]*	36	Streptokinase	Intracoronary	5 of 36†	No
Gold et al[36]	12/12	rt-PA	Intravenous	Yes	Yes
Gotoh et al[37]	37	Urokinase	Intracoronary	If thrombus	No
De Zwaan et al[38]	41	Streptokinase or rt-PA	Streptokinase IC; rt-PA IV	If stenosis >90%†	No
Schreiber et al[39]	12/13	Urokinase	Intravenous	No	Yes
Nicklas et al[40]	20/20	rt-PA	Intravenous	No†	Yes/No
Ardissino et al[41]	12/12	rt-PA	Intravenous	No†	Yes
Williams et al[42]	45/22	rt-PA	Intravenous	No†	No
Freeman et al[43]	35/35	rt-PA	Intravenous	No†	No

*Study includes patients with non-Q-wave infarction.
†Study using quantitative coronary arteriographic measurements as an end point.
IC = intracoronary; IV = intravenous; rt-PA = recombinant tissue-type plasminogen activator.

When combined, these studies suggest that any improvement in the severity of stenosis induced by thrombolysis is likely to be limited to totally or subtotally occluded arteries or arteries with obvious thrombus. Even then, thrombolysis may not be superior to standard therapy with heparin and aspirin. Small improvements in a critically narrowed lesion may be difficult to detect arteriographically, but may have important functional consequences. Nicklas et al[40] reported that rt-PA patients with obvious thrombus had a decrease in stenosis diameter from a mean of 82% to 73% which was associated with an increase in their pacing threshold to ischemia of 26±7 beats/min.

Ultimately, whether thrombolysis becomes a routine component of therapy for unstable angina depends on whether it can prevent angina or MI, or improve long-term outcome. In the controlled studies that reported death or myocardial infarction,[39–42] one of these events occurred in 11 of 88 thrombolysis patients and 8 of 67 controls (12.5% vs 11.9%, respectively). The sample sizes of these studies are too small to detect even a modest benefit for this end point. At least one study in progress, Thrombolysis in Myocardial Infarction-III (TIMI-III), should be large enough to settle this question.

Other agents with different mechanisms of action: Ticlopidine is a platelet inhibitor with an incompletely understood mechanism of action; it appears to interfere with fibrinogen and von Willebrand factor interactions with the glycoprotein receptor IIb/IIIa.[44] In a randomized, nonblinded study of 652 patients with unstable angina, ticlopidine reduced the incidence of vascular death plus nonfatal infarction, from 13.6% to 7.3% (p=0.009), a 46% risk reduction.[45] Patients were enrolled within 48 hours of admission and followed for 6 months. Ticlopidine also prevents periprocedural complications of angioplasty[46] and improves coronary bypass graft patency.[47] In a large multicenter stroke prevention study, ticlopidine was superior to aspirin but had more serious adverse effects.[48] In the management of unstable angina and in coronary disease, aspirin appears to be as effective as ticlopidine.

Monoclonal antibodies to the glycoprotein IIb/IIIa receptor prolong bleeding time and inhibit platelet aggregation[49]; these antibodies hold promise both for the treatment of unstable angina and as adjunctive therapy with thrombolysis.[50] Prostacyclin (prostaglandin I_2), a potent vasodilator and platelet inhibitor produced by vascular endothelium, is ineffective in unstable angina at doses that inhibit platelet aggregation.[51]

Low molecular weight heparin is currently undergoing clinical evaluation. Compared with standard heparin, it causes less bleeding at equal antithrombotic doses, and thus can be given to outpatients without rigorous monitoring. More potent thrombin inhibitors, such as hirudin,[52] will soon be available for clinical trials. This product of recombinant DNA technology prevents formation of Factors V, VIII and XIII, blocks thrombin-induced platelet activation and, in contrast to heparin, inactivates fibrin-like thrombin.

Role of revascularization: The majority of patients with unstable angina have multivessel disease, often associated with exercise-induced myocardial ischemia or some degree of left ventricular dysfunction. Stable angina patients with these characteristics have improved survival with coronary artery bypass surgery.[53,54] After an episode of unstable angina, many patients remain limited by typical angina in spite of medical therapy; if coronary anatomy is favorable, coronary bypass surgery can relieve this symptom in 90% of such patients.

Two controlled clinical trials have compared medical and surgical therapy in unstable angina.[55,56] Between 1972 and 1976, the National Cooperative Study Group enrolled 288 patients.[55] The in-hospital mortality rate was 5% for surgical and 3% for medical patients (difference not significant); 17% of the surgical and 8% of the medical patients developed MI in the hospital ($p<0.05$). After 1 year of follow-up, medically treated patients were more limited by angina, irrespective of whether they had single, double, or triple vessel disease. After a mean follow-up of 30 months, mortality was similar in the 2 groups, and 36% of the patients initially assigned to medical therapy had undergone surgery because of an unacceptable level of angina.

The results of this trial cannot be applied to clinical practice today because of the important advances in both medical and surgical treatments that have occurred in the intervening years. The Veterans Administration Cooperative Study, which enrolled 468 patients between 1976 and 1982, is more recent and more relevant.[56] The operative mortality rate was 4.1% and the graft patency rate at 1 year was 75%. Within 2 years, 34% of the medically assigned patients had crossed over to surgery. By 5 years, survival in the medical patients was 81% compared to 84% in surgical patients (difference not significant).

However, a definite benefit was seen with surgery in those patients with the most severe coronary disease: 5-year mortality with triple vessel disease was 11% with surgery and 24% with medical therapy ($p<0.02$).[57] The advantage was even larger for patients with triple vessel disease and left ventricular dysfunction: 9% mortality with surgery and 29% with medical treatment ($p<0.05$). Many of the sickest patients (age ≥70 years, left main stenosis, severe left ventricular dysfunction, previous bypass surgery, recent MI) were excluded from this study. However, such patients will often benefit from surgery as well. Although surgery relieves angina, and in certain subsets improves survival, it does not reduce the risk of MI.[57]

Table VI lists the characteristics of unstable angina patients undergoing bypass surgery and the general results for over 6,000 patients in 14 reports published between 1978 and 1988.[58] Despite a high prevalence of triple vessel involvement, left main stenosis and previous infarction in this population, the results are good, with 5-year survival ranging from 85% to 92%. Even better results have been reported from single institutions: Rahimtoola et al[59] reported a 1.8% operative mortality with 83% 10-year survival. The 10-year reoperation rate was 17%, and 61% of survivors were angina-free at latest follow-up. Improved myocardial protection techniques and greater use of internal thoracic (mammary) artery grafts have improved surgical results since these studies were performed. However, improved results are not reflected in surgical statistics because older and sicker patients are now frequently referred for operation.

TABLE VI Results of Coronary Bypass Surgery for Unstable Angina*

	Mean (%)	Range (%)
Patient characteristics		
3-vessel disease	52	16–75
Left main stenosis	19	0–35
Previous infarction	50	38–67
Operative mortality	3.7	1.2–8.5
Perioperative infarction	9.8	3.8–17
Survival to 5 years	88	85–92

*Fourteen reports from 1978 to 1988 of 6,136 patients with unstable angina undergoing bypass surgery.
Adapted from *Circulation*.[58]

Coronary angioplasty appears to be ideal therapy for unstable angina patients with single vessel disease, even through controlled clinical trials are not yet available to support this claim. Coronary angioplasty can also be applied to selected unstable angina patients with multivessel disease, either by dilating multiple lesions or by limiting angioplasty to the ischemia-producing stenosis.[60–62] The risk of angioplasty is higher in unstable than in stable angina patients and increases even further when the procedure is done soon after the onset of symptoms.[62] Successful angioplasty can be anticipated in 80–90% of unstable angina patients with suitable anatomy.[60–62] Between 5% and 10% will develop MI or require emergency bypass surgery as a result of the procedure.[60,61] Unstable angina is probably a risk factor for restenosis—the primary limitation of coronary angioplasty. An improvement in segmental left ventricular function distal to successfully dilated arteries has been demonstrated in unstable angina, presumably due to reversal of myocardial stunning.[63]

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Intravenous Diltiazem Versus Nitroglycerin for Silent and Symptomatic Myocardial Ischemia in Unstable Angina Pectoris

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For 18 patients consecutively admitted to the coronary care unit for unstable angina, 48-hour electrocardiographic Holter monitoring was performed after they were randomly assigned in a single-blind fashion to 1 of 2 treatment groups. The first group was treated with acetylsalicylic acid (ASA) and intravenous nitroglycerin, the second with ASA and intravenous diltiazem. All of the patients treated with nitroglycerin still had ischemic episodes after 48 hours (33% were symptomatic), in contrast with 11% of the diltiazem group (11% asymptomatic). Maximal ST-segment depressions of symptomatic and asymptomatic episodes were significantly different; and no significant increases in heart rate were observed either during the 15 seconds before ischemia began or during the ischemic episode. During the 48 hours, the diltiazem group had significantly fewer ischemic episodes (17) than did the nitroglycerin group (145). We concluded that "on-line" ST-segment observation is of prime importance for monitoring unstable angina; that the majority of the ischemic episodes associated with unstable angina are silent; and that intravenous diltiazem could be an effective pretreatment for patients who must undergo mechanical or surgical therapy.

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It has long been recognized that unstable angina is associated with a high incidence of serious adverse clinical outcomes, i.e., refractory symptoms requiring myocardial revascularization, acute myocardial infarction, or sudden death.[1–4] Continuous in-hospital electrocardiographic monitoring of patients with unstable angina has shown that as many as 80–90% of episodes of ST-segment depression occur without any chest pain.[5–7] Further, several investigators have provided evidence that silent myocardial ischemia adversely affects the prognosis of these patients.[8–10]

According to Cohn,[11] nitrates or calcium antagonists could provide the best therapy for episodes of silent ischemia not associated with increased myocardial work load. Calcium antagonists have been shown to be useful for relieving symptoms in patients with unstable angina, although they appear to have limited effectiveness as therapy for silent myocardial ischemia.[12–15] Very few studies have reported on the effectiveness of intravenously administered calcium antagonists.

Salvade et al[12] and Mauri et al[16] have suggested that intravenous diltiazem and verapamil may be effective for managing both unstable angina and silent myocardial ischemia.

The present study was designed to compare diltiazem with nitroglycerin when administered intravenously to patients with unstable angina. It was conducted in the coronary care unit with 18 patients who had coronary artery disease documented by history, electrocardiogram (ECG), and angiography, and for whom acute myocardial infarction had been ruled out by serial serum creatine kinase MB (CK-MB) determinations. Patients underwent coronary angiography within 10 days of beginning the study. All patients gave informed consent before study entry, and the study protocol was approved by the Hospital Ethical Committee.

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TABLE I Patient Characteristics, Nitroglycerin Group

			Coronarography		
Patient No.	Sex/Age* (Yr)	ECG Ischemia Localization	Left Anterior Descending (%)	Circumflex Coronary Artery (%)	Max 10 Days Delay, Right Coronary Artery (%)
1†	M/52	Anteroseptal	DA (E+)	DA	DA
2†‡§	F/69	Anteroseptal‖	100	100	80
3†‡§	M/55	Anterior‖	100	100	50
4†	F/66	Anteroseptal	DA (E+)	DA	DA
5†‡	F/48	Anterolateral	95	90	90
6†	M/50	Anterolateral	90	70	80
7†	M/52	Anteroseptal	80	80	70
8†	M/62	Anteroseptal	70	85	50
9†	M/57	Anterior	85	70	50

*Mean ± standard deviation 56.8 ± 6.0.
†Asymptomatic angina after 48 hours.
‡Symptomatic angina after 48 hours.
§Previous myocardial infart; coronary artery bypass graft.
‖Acute myocardial infarction after 48 hours waiting for surgery.
DA = diffuse at positive ergonovine test; ECG = electrocardiographic; E+ = positive ergonovine test.

PATIENTS AND METHODS

The 18 patients, 12 men and 6 women, aged 48–70 years (mean age 59.5±6.5 years), were consecutively hospitalized in the coronary care unit for unstable angina. The diagnosis of unstable angina was based on the occurrence of repetitive episodes of angina at rest, accompanied by >1.5-mm ST-segment depression. Patients were excluded from the study if they had any of the following: a heart rate of ≤50 beats/min, 2nd or 3rd degree atrioventricular block, amiodarone treatment during the previous 6 months, systolic blood pressure >170 mm Hg or <100 mm Hg, clinical signs of heart failure, or chest pain that was unresponsive to sublingual nitroglycerin.

Patients were randomly assigned, in a single-blind manner, to receive either intravenous nitroglycerin or diltiazem, which resulted in 2 groups of comparable age (58.3±7.8 years for the nitroglycerin group, and 61.0±5.1 years for diltiazem). During the 24 hours before the study began, medication was restricted to 300 mg of aspirin by mouth, intravenous heparin, and sublingual nitroglycerin or nifedipine to relieve anginal symptoms. General characteristics of the patients are summarized in Tables I and II.

Continuous ST-segment monitoring was obtained by using a 2-channel system (Avionics 750) meeting the recommendations of the Committee on Clinical Cardiology published by the American Heart Association.[17] Calibration included assessing the influences of body position and of maximal inspiration and expiration on ST-segment shift from baseline measurements. Only episodes of >0.1 mV, 0.06–0.08 seconds beyond the peak of the R wave, were considered for analysis in this study. All patients remained supine throughout the study. The 48-hour ECG strips were analyzed by an independent observer who was unaware of treatment allocation.

Cardiac rhythm was monitored and analyzed "on-line" by a standard Hewlett-Packard com-

TABLE II Patient Characteristics, Diltiazem Group

			Coronarography		
Patient No.	Sex/Age* (yr)	ECG Ischemia Localization	Left Anterior Descending (%)	Circumflex Coronary Artery (%)	Max 10 Days Delay, Right Coronary Artery (%)
1§	F/67	Anteroseptal	85	100	85
2§	M/69	Anterolateral	90	0	100
3‡§	M/61	Anterolateral	90	85	100
4	F/60	Anterolateral	95	DA	60
5	M/52	Anteroseptal	DA (E+)	DA	DA
6	M/58	Anterolateral	80	70	0
7§	M/64	Anterior	80	80	100
8	F§/60	Anteroseptal	70	90	50
9	M/58	Anterior	90	0	50

Symbols as in Table I.

TABLE III Comparison of Ischemic Episodes in Nitroglycerin and Diltiazem Groups

	Nitroglycerin				Diltiazem			
	24 Hours		48 Hours		24 Hours		48 Hours	
Ischemic Episodes	No. of Pts.	%	No. of Pts.	%	No. of Pts.	%	No. of Pts.	%
Symptomatic	5	55	3	33	3	33	0	0
Asymptomatic	9	100	9	100	5	55	1	11

0.01

0.05

puter (HP21MXE system computer). After randomization, a 48-hour infusion of nitroglycerin or diltiazem was begun for all patients, starting with 2.5 mg/hr of nitroglycerin or 10 mg/hr of diltiazem. Hourly infusion rates were increased by 0.25 mg of nitroglycerin and 5 mg of diltiazem after each episode of angina, up to a maximum of 5.0 mg/hr of nitroglycerin and 20 mg/hr of diltiazem.

If anginal symptoms persisted at the highest dose, treatment was considered to have failed and was discontinued. Appropriate medical, mechanical, or surgical treatment was then instituted.

STATISTICAL ANALYSIS

Comparisons of the influence of both treatments on symptom relief and on silent ischemic episodes, as evidenced by ST-segment shifts, were obtained by means of chi-square analysis. Student's *t* test adapted for small groups was used to analyze unpaired variables.

RESULTS

In the nitroglycerin-treated group, coronary angiography performed within 10 days of the onset of unstable angina showed that 2 patients had diffuse coronary atherosclerosis and a positive ergonovine test, no patient had single-vessel disease or 2-vessel disease, and 7 patients had 3-vessel disease. In the diltiazem-treated group, coronary angiography found 1 patient with diffuse coronary atherosclerosis, 4 patients with 2-vessel disease, and 4 patients with 3-vessel disease.

Holter monitoring during the 48-hour observation period showed persistent ischemia in all patients treated with intravenous nitroglycerin, although only 3 of these patients (33%) were symptomatic (Table III). In contrast, in the diltiazem-treated group, only 1 Holter recording showed persistent ischemic episodes over 48 hours, and all patients were asymptomatic. These differences reached statistical significance (Table III).

The total number of ischemic episodes (Tables IV and V) was significantly greater ($p < 0.05$) in the nitroglycerin-treated patients (145 episodes) compared with the diltiazem-treated patients (17 episodes). Mean maximal ST-segment depression (no episodes of ST-segment elevation were detected) was significantly greater during anginal episodes (3.7±1 mm) than during silent ischemia (2.7±1 mm; $p < 0.5$). Although there were no significant differences in maximal heart rates during symptomatic and asymptomatic episodes, maximal heart rates during ischemia were significantly lower with diltiazem than with nitroglycerin therapy ($p < 0.05$). Finally, mean heart rates during ischemia and during the 15 seconds before its onset were not significantly different from mean basal heart rates during the corresponding diurnal or nocturnal periods.

DISCUSSION

Studies of patients with silent ischemia can improve our understanding of the pathophysiology of the syndrome and lead to the development of new ways to treat it.[18-21] Our observation that heart rate did not increase either before or during ischemia suggests that an imbalance in coronary blood supply is one of the major mechanisms contributing to the myocardial ischemia of unstable angina.

The results of several studies have suggested that while vasodilators effectively suppress anginal symptoms, they less effectively control asymptom-

TABLE IV Effects of Nitroglycerin Therapy on Ischemia

	Episodes				
Ischemic Episodes	No. of Pts.	%	Duration of Episodes (minutes) (Mean ± SD)	Heart Rate (beats/min) (Mean Max ± SD)	ST-Segment Depression (min) (Mean Max ± SD)
Symptomatic	11	8	4.6 ± 1.5	85 ± 5.7	4.0 ± 0.9
Asymptomatic	134	92	6.9 ± 3.0	86 ± 6.0	3.0 ± 1.1
Significance		0.001	0.05	NS	0.05

Max = maximal; NS = difference not significant; SD = standard deviation.

TABLE V Effects of Diltiazem Therapy on Ischemia

Ischemic Episodes	Number of Episodes		Duration of Episodes (minutes & seconds) (Mean ± SD)	Heart Rate (beats/min) (Mean Max ± SD)	ST-Segment Depression (min) (Mean Max ± SD)
	No. of Pts.	%			
Symptomatic	3	18	4.6 ± 1.7	62 ± 4.3	3.5 ± 1.0
Asymptomatic	14	82	8.3 ± 6.2	59 ± 5.0	2.5 ± 1.3
Significance		0.001	0.05	NS	0.05

Max = maximal; NS = difference not significant; SD = standard deviation.

atic ischemic episodes of unstable angina.[6,19–21] That suggestion was confirmed in the present study by the nitroglycerin-treated patients; in contrast, diltiazem therapy suppressed both symptomatic and asymptomatic ischemic episodes. This observation may be clinically relevant, because the persistence of silent ischemia has been shown to adversely affect the outcome for patients with unstable angina.[6,19–21]

Parodi et al[21] reported a 60% reduction in asymptomatic episodes among patients on an oral-therapy regimen combining isosorbide dinitrate (300 mg/day) and verapamil (240–400 mg/day). Similar results were reported by others when combining verapamil or nifedipine with isosorbide dinitrate,[16] or nifedipine with propranolol.[20] A combination of intravenous nitroglycerin and heparin, plus diltiazem or verapamil may achieve an even higher suppression rate.[16] Our study confirms that intravenous diltiazem and oral aspirin are more effective for controlling both silent and symptomatic ischemia than are intravenous nitroglycerin and aspirin. Indeed, 48 hours after beginning treatment, all of the patients taking nitroglycerin continued to have silent ischemic episodes, but 89% of the patients taking diltiazem were free of silent ischemia. As already noted, the diltiazem group had only 17 ischemic episodes during the study period, whereas the nitroglycerin group had 145. Mean heart rates with diltiazem therapy were lower than with nitroglycerin treatment, thereby reducing the myocardial oxygen demand. Reducing oxygen demand could, along with the vasoactive effects of diltiazem, explain the superior therapeutic effect of intravenous diltiazem on both silent and symptomatic ischemia. Tolerance to nitrates could also account for the poor results observed with nitroglycerin. The symptomatic episodes were briefer than the silent ones, presumably related to the study protocol, which called for immediate treatment of anginal episodes, whereas silent ischemia went unnoticed before the analysis of the tapes. No patient developed an acute myocardial infarction during the study period, and there were no treatment-related dropouts.

LIMITATIONS AND CONCLUSION

Although our study was not double blind and no crossover treatment was performed, we believe that the results are clinically relevant. Indeed, the single-blind randomization scheme may have been compensated for by the objective ECG analyses performed by independent observers unaware of treatment allocations. Moreover, while the crossover design allows comparisons of different treatment regimens with the same patient, its implementation requires a placebo period between treatment phases to ensure proper drug washout and to document persistent instability of the anginal symptoms. The high morbidity and mortality associated with unstable angina make placebo treatment unacceptable.

Our study confirms the observation that the vast majority of ischemic episodes in unstable angina are asymptomatic, emphasizing the usefulness of on-line ST-segment monitoring. The data support the hypothesis that vasospasm plays an important role in unstable angina, and they also demonstrate the therapeutic effectiveness of intravenously administered diltiazem for unstable angina.

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Treatment of Unstable Angina Pectoris (European Experience)

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Unstable angina pectoris is used to describe accelerated angina, new onset of angina, or prolonged angina. The natural history of the angina varies according to clinical presentation. The 1-year mortality rate ranges from 2% to nearly 40%. Specific therapy includes nitrates, β-adrenergic blockers, and/or calcium antagonists as well as antithrombotic therapy in the form of aspirin. Patients with severe angina at rest and ST- and T-wave changes should be admitted to a coronary care unit where full-dose heparin is administered. Coronary angiography should be performed in individuals who fail to respond to the conventional therapy in order to evaluate other therapeutic options, including percutaneous transluminal coronary angioplasty (PTCA) and coronary bypass surgery. In some cases, especially in patients with intracoronary thrombus, thrombolytic therapy may be beneficial.

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The term "unstable angina" is generally used to describe different clinical conditions, such as accelerated angina pectoris (with increase of severity and frequency of known chronic angina), new onset of angina, and prolonged angina associated with ST-segment and T-wave changes. The prognosis of patients with any of these clinical syndromes differs considerably, with the worst in the prolonged angina group. Therefore, the management of unstable angina, including the aggressiveness and timing of interventional techniques, initially depends on the clinical presentation.

This report will first briefly discuss the treatment of unstable angina with antithrombotic drugs, antiischemic agents, and intervention techniques, and then will cover our experience with coronary interventions in the Department of Cardiology of the University of Saarland in Homburg/Saar.

ANTITHROMBOTIC THERAPY

Rupture of an atherosclerotic plaque with platelet aggregation and thrombus formation, as occurs in Q-wave and non-Q-wave infarction, plays a major role in unstable angina.[1] Heparin and aspirin can prevent fatal and nonfatal myocardial infarction (MI).[2–4] In a recently published study, ticlopidine, an inhibitor of platelet aggregation that is completely different from aspirin, also significantly reduced vascular death and nonfatal MI in patients with unstable angina.[5] Antithrombotic therapy must be started in the early phase of unstable angina.

ANTIISCHEMIC THERAPY

Beta-adrenergic blockers or calcium antagonists, in combination with nitrates, are widely used to treat unstable angina, despite the lack of data showing that antiischemic therapy reduces mortality or the rate of infarction. However, the beneficial effect of reducing ischemic episodes is clear-cut.[6–9] Available reports show that β-adrenergic blockers or calcium antagonists such as diltiazem and verapamil are equally effective in preventing ischemia

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and can be used as monotherapy.[8,9] In addition, diltiazem reduced the reinfarction rate in patients with non-Q-wave infarction,[10] which is pathogenetically similar to unstable angina.[11] However, nifedipine as monotherapy should be avoided because of increased adverse cardiac events.[7,12] On the other hand, nifedipine is safe and effective as part of combination therapy when the symptoms are not controlled with β-adrenergic blockers.[7,13,14]

CORONARY INTERVENTIONS

Thrombolytic therapy: Since intracoronary thrombi are frequently detected in patients with unstable angina, investigators have become interested in the applicability of thrombolytic therapy.[15-29] Some have found only mild quantitative and qualitative effects of thrombolytic therapy,[23,25,28] whereas others report symptomatic and clinical improvement.[16,22,24,26] In a randomized, double-blind, placebo-controlled study of 24 patients with unstable angina, defined as chest pain at rest with transient ST-segment deviation of at least 1 mm, no coronary thrombi were found in patients treated with recombinant tissue-type plasminogen activator (rt-PA) compared with 8 of 11 placebo-treated patients.[22] Further, recurrent angina occurred in only 1 actively treated patient compared with 6 in the placebo group. Nicklas et al[27] noted additional benefits of thrombolysis in combination with maximal therapy. The benefit was limited, however, to patients with angiographic evidence of intracoronary thrombus.

A prospective study was performed in our institution to determine whether thrombolysis in patients with unstable angina and evidence of intracoronary thrombi would beneficially affect outcome.[30] Thirty-one patients (26 male and 5 female, mean age 60±11 years) with intermittent electrocardiographic abnormalities during chest pain (ST depression in 17 patients, ST elevation in 10, and T inversion in 9) who were unresponsive to the standard therapy, including full-dose intravenous heparin, underwent coronary angiography within 12 hours after admission to the intensive care unit. Fifteen patients had 1-vessel disease, 10 had 2-vessel disease, and 6 had 3-vessel disease. Intracoronary thrombus was visualized in 13 patients (Figure 1). Percutaneous transluminal coronary angioplasty (PTCA) was performed in 17 of 18 patients without angiographic evidence of thrombus (1 patient had emergency surgery because of left main stenosis), and thrombus was detected in 6. All 19 patients with evidence of thrombi were treated with intravenous rt-PA at a dose of 10 mg as a bolus, followed by continuous infusion of 10 mg/hr over 9 hours (Figure 1). Control angiography performed within 24 hours (n=15) showed complete lysis of thrombi in 10.patients and partial lysis in 5. More importantly, subsequent PTCA (n=5) was without any complications in 4 patients with complete thrombolysis and 1 patient with partial thrombolysis. One other patient underwent coronary bypass surgery electively. In the remaining 9 patients a substantial decrease of stenosis was observed and there were no indications for further coronary interventions.

Coronary angioplasty: PTCA was initially attempted only in those patients with 1-vessel disease and in those with a single, proximal, noncalcified lesion of a major epicardial coronary artery whose angina was relatively resistant to medical therapy. Recently, increasing numbers of patients with unstable angina have undergone PTCA in many centers.[31-36] The initial success rate of PTCA appears to be slightly lower and the acute complication rate higher in unstable versus stable angina.

Between January 1 and December 1, 1990, PTCA was performed in our center in 1,092 patients: 755 with stable angina and 337 with unstable angina. Most of the patients with unstable angina

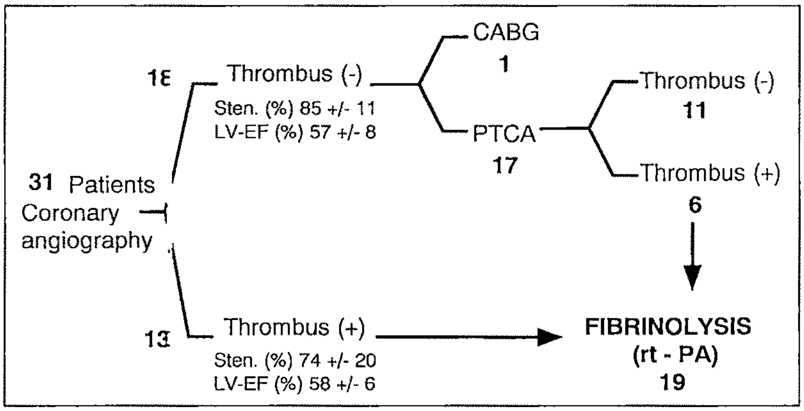

FIGURE 1. The rate of intracoronary thrombus detected by urgent coronary angiography before and after percutaneous transluminal coronary angioplasty (PTCA) in 31 patients with unstable angina unresponsive to the conventional therapy. Sten = coronary stenosis; LV-EF = left ventricular ejection fraction; CABG = coronary artery bypass graft; rt-PA = recombinant tissue-type plasminogen activator.

TABLE I Angiographic Findings of Patients (n = 1,092) Undergoing Coronary Angioplasty During 1990 in Homburg/SAAR

	SA (n = 755)		UA (n = 337)		p Value
SVD (n)	272	(36%)	124	(37%)	NS
DVD (n)	274	(36%)	119	(35%)	NS
TVD (n)	209	(28%)	94	(28%)	NS
LVEF (%)	58		57		NS
Intraluminal filling defect (n)	65	(9%)	83	(25%)	<0.001

DVD = double-vessel disease; TVD = triple-vessel disease; SA = stable angina; UA = unstable angina; SVD = single-vessel disease; LVEF = left ventricular ejection fraction; NS = difference not significant.

had prolonged chest pain and transient ST-segment and T-wave abnormalities documented at least once during the 4 weeks preceding. Tables I, II, and III show coronary angiography findings, acute results of PTCA and incidence of acute complications. Intracoronary filling defects and the number of PTCA of proximal left anterior descending artery lesions, which appeared responsible for angina, were significantly higher in patients with unstable angina compared with stable angina. The incidence of acute complications was slightly higher in unstable angina; however, the difference was not statistically significant.

Our experiences and that of other investigators indicate that PTCA can be performed safely in patients with unstable angina. The high incidence of acute complications in this group[34,35] may be decreased in the near future by better selection of patients and advances in medical therapy and interventional materials. The long-term prognosis after successful PTCA seems to be excellent.[34,36]

TABLE II Coronary Angioplasty During 1990 Homburg/Saar

	SA (n = 755)		UA (n = 337)		p Value
Dilated artery (n)					
LM	1		1		
LAD	466	(62%)	223	(66%)	NS
Proximal LAD	133	(18%)	93	(28%)	<0.001
LCX	268	(36%)	109	(32%)	NS
RCA	259	(34%)	122	(36%)	NS
CABG	12	(1.6%)	5	(1.5%)	NS
Dilated stenoses per patient (n)	1.33		1.36		NS
Dilated stenoses per procedure (n)					
1	757	(75%)	340	(74%)	
2	187	(19%)	93	(20%)	
3	55	(5%)	25	(5%)	NS
4	6		2		
5	2			—	
Diameter stenosis (%)					
Before	82.7%		84.4%		NS
After	26.4%		28.4%		NS

CABG = coronary artery bypass graft; LAD = left anterior descending; LCX = left circumflex artery; LM = left main coronary artery; NS = difference not significant; RCA = right coronary artery; SA = stable angina; UA = unstable angina.

TABLE III Incidence of Complications of Coronary Angioplasty Performed in 1990 in Homburg/Saar

	SA (n = 755)		UA (n = 337)		p Value
AOS (n)	27	(3.6%)	15	(4.5%)	NS
AMI (n)	20	(2.7%)	11	(3.3%)	NS
CABG surgery <3 days (n)	1	(0.1%)	1	(0.3%)	NS
Death (n)	2	(0.3%)	4	(1.2%)	NS

UA = unstable angina; AMI = acute myocardial infarction; AOS = acute occlusion syndrome; CABG = coronary artery bypass graft; ns = difference not significant; SA = stable angina.

CONCLUSIONS

The successful management of unstable angina requires a variety of different therapeutic approaches. Figure 2 illustrates our present protocol. Patients suffering from unstable angina, especially those with prolonged chest pain associated with electrocardiographic abnormalities, are admitted to the intensive care unit and every effort is made toward stabilization. Therapy is started with an intravenous bolus of 5,000 IU heparin followed by continuous infusion of 18 IU/kg/hr. The dose is adjusted according to the activated partial thromboplastin time (range, 2–3 times higher than normal value). If a patient has been receiving aspirin, it is continued. In others, aspirin is withheld during the first few hours until the possibility of coronary bypass surgery has been excluded, because the presence of aspirin significantly increases the risk of bleeding complications.[37] Further, aspirin plus heparin is not superior to heparin alone in reducing fatal and nonfatal MI in unstable angina.[3] In addition to heparin, nitrates in combination with calcium antagonists and/or β-blockers are administered. If the patient is stabilized by conventional

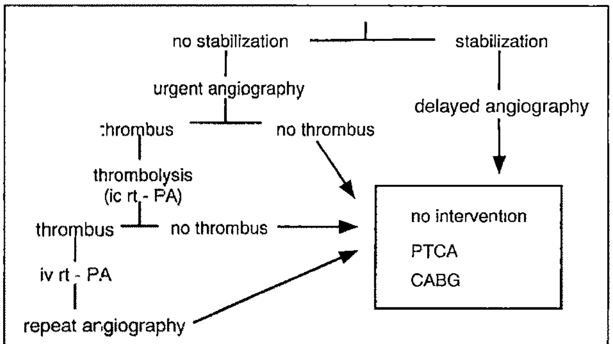

FIGURE 2. Proposed schema for the management of patients with unstable angina. ic = intracoronary; iv = intravenous; PTCA = percutaneous transluminal coronary angioplasty; CABG = coronary artery bypass graft; rt-PA = recombinant tissue-type plasminogen activator.

therapy, aspirin is added to the therapeutic regimen and the patient is transferred to the normal care station. Intravenous heparin is continued for at least 3 days. Coronary angiography is performed usually after 8 to 10 days. Patients who do not respond to initial stabilization therapy undergo emergency angiography. In those with intracoronary thrombi thrombolytic treatment is started for symptomatic stabilization, and PTCA as adjunctive therapy.[38–40] An intracoronary injection of rt-PA is used in a dose of 20–40 mg. If complete lysis is achieved, PTCA is performed depending on the residual stenosis and flow grade. If thrombi persist, therapy is continued intravenously in a dose of 10 mg/hr up to a total dose of 100 mg. Angiography is repeated within 24–36 hours. Depending on the coronary morphology, patients are either treated conservatively without further interventions, or undergo PTCA or bypass surgery.

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Calcium Antagonists and Left Ventricular Function

J. Thomas Heywood, MD

Calcium antagonists impede the entry of calcium into myocytes and inhibit myocardial contraction. Calcium antagonists differ in their relative negative inotropic potency and can provoke baroreceptor stimulation that modulates left ventricular (LV) performance. Calcium antagonists are uniformly well tolerated in patients with normal LV function. Use of these agents in patients with suspected LV function impairment has yielded results ranging from hemodynamic improvement to clinical deterioration and increased mortality. Reports of clinical deterioration when calcium antagonists were combined with β blockers underscore the importance of reflex adrenergic support for the myocardium. Although calcium antagonists are potent vasodilators and produce short-term hemodynamic improvement, they are not useful as primary treatment in patients with congestive heart failure (CHF). They may have a place in the treatment of coexistent problems in patients with LV dysfunction. Short-term use of calcium antagonists for myocardial ischemia or rapid atrial fibrillation is probably safe in the presence of LV dysfunction and overt CHF. Calcium antagonists appear to have a role in the treatment of patients with diastolic dysfunction of diverse etiologies.

(Am J Cardiol 1991;68:52C–57C)

In the 30 years since their discovery, calcium antagonists have become extremely important in treating cardiovascular disease.[1] Early in their evaluation, indeed even before their mode of action was elucidated, these agents were recognized as potent inhibitors of myocardial contraction.[2] Thus, there was initial caution in employing them when impairment of left ventricular (LV) function was suspected. As the usefulness of calcium antagonists in treating a wide range of disorders (including hypertension, arrhythmias, and angina pectoris) became apparent, however, investigators began to evaluate them in patients with depressed LV function.[3] These efforts have yielded a wide range of results, from marked hemodynamic improvement to clinical deterioration and increased mortality. Clearly, it would be useful to employ calcium antagonists, at least selectively, in patients with decreased LV function. Can this be done safely? Are these agents uniformly deleterious in patients with abnormal LV function, or are there specific clinical situations in which they are beneficial?

CALCIUM ANTAGONISM AND NORMAL LV FUNCTION

Calcium antagonists vary widely in their effect on LV function. Böhm et al[4] evaluated the effects of equimolar concentration of nifedipine, diltiazem, verapamil, nitrendipine and isradapine on LV papillary muscles removed from patients undergoing mitral valve replacement. There was more than a 20-fold difference in the relative potency of negative inotropic effects among these agents (Figure 1). Nifedipine was the most potent negative inotrope on a molar basis, followed by verapamil, diltiazem, nitrendipine, and isradapine. The latter two agents, in particular, are almost pure arteriolar dilators with very minimal effects on the ventricular myocardium in micromolar concentration. The concentration of the calcium antagonists were typically 3–5 times higher than published therapeutic ranges in patients. This is important because it implies that these agents can cause significant

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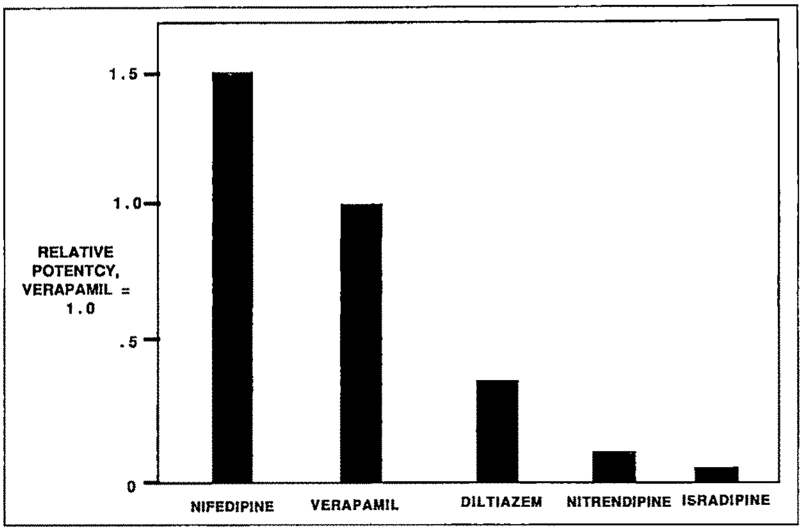

FIGURE 1. Equimolar amounts of various calcium antagonists were placed in a solution bathing papillary muscles obtained from patients undergoing mitral valve replacement. The relative effects of each agent on myocardial contraction are shown. Data from *Am J Cardiol*.[4]

arterial dilation in patients at concentrations that ordinarily do not cause significant depression in LV contractility.

Not only do calcium antagonists differ in their relative negative inotropic potency, they provoke baroreceptor stimulation that can modulate LV performance. Thus nifedipine, the most potent negative inotrope of the calcium antagonists, actually produces an increased ejection fraction and peak *dP*/*dt* in patients with normal LV function.[5] This apparent improvement in LV function is a result of reduced afterload and reflex adrenergic stimulation.[6] When these reflexes are blocked pharmacologically, nifedipine causes a decline in maximum *dP*/*dt*.[7] The importance of reflex adrenergic support for the myocardium when calcium antagonists are used is underscored by reports of clinical deterioration when these drugs are combined with β receptor antagonists.[8] In patients with normal LV function, however, the calcium antagonists are uniformly well tolerated.

USE OF CALCIUM ANTAGONISTS IN PATIENTS WITH IMPAIRED LEFT VENTRICULAR FUNCTION

Nifedipine: This agent is predominantly an arteriolar vasodilator with very little effect on the venous capacitance vessels.[9] In reviewing 9 studies (total 131 patients) of nifedipine in congestive heart failure (CHF), Colucci et al[10] noted that nifedipine produced a significant reduction in systemic and pulmonary vascular resistance, with a concomitant rise in cardiac index. Overall changes in right atrial pressure and pulmonary capillary wedge pressure were small. Ludbrook et al[11] noted that in patients with higher resting LV end-diastolic pressures, nifedipine caused a decrease in LV end-diastolic pressure. Similar significant reductions in the wedge pressure were seen in patients with acute pulmonary edema who were given nifedipine.[12]

Unfortunately, patients given nifedipine have also deteriorated clinically. In a comparative study of diltiazem and nifedipine in 21 patients with significant CHF, a marked reduction in systemic vascular resistance occurred with nifedipine, but LV filling pressure did not change. More notably, 6 of 21 patients given nifedipine suffered clinical worsening of their CHF.[13] In the same group of patients, only 1 of 21 deteriorated on diltiazem. Elkayam et al[14] reported that one third of patients with severe CHF (mean ejection fraction 17%) worsened after nifedipine administration (Figure 2).

It is unclear why some patients deteriorate with nifedipine therapy. In the study by Elkayam et al,[14] hemodynamic parameters were not useful in predicting which patients would worsen with this therapy, although younger patients appeared to do better than older patients. The group of patients studied had very severe heart failure, so it is possible that small reductions in myocardial contractility were poorly tolerated. Unlike the normal ventricle, maximum *dP*/*dt* falls with nifedipine administration in patients with CHF, most likely because they already have increased adrenergic tone that does not increase further following nifedipine.[9]

Verapamil: The negative inotropic effects of verapamil have long been appreciated, and so it was believed that this drug should not be used in patients with LV dysfunction. Therefore, investigations of such patients have been limited. Verapamil, when given to patients with angina pectoris and a mean ejection fraction of 40%, produced an improvement in exercise tolerance.[15] Ferlinz and Citron[16] administered verapamil to 14 patients with

CHF. Systemic vascular resistance decreased whereas ejection fraction and cardiac index increased significantly.

As has been observed with nifedipine, some patients receiving verapamil deteriorate. Chew et al[17] reported deterioration with administration of verapamil to 20 patients with ejection fractions < 35% and wedge pressures > 20 mm Hg. In another study, verapamil had to be withdrawn in 4 of 9 patients with CHF because of clinical deterioration.[18] Verapamil causes a decrease in peak *dP/dt* in impaired ventricles. Although this negative inotropic effect is offset in moderately impaired ventricles by a balanced reduction in afterload, it should probably not be used in patients with ejection fractions <35% and clinical evidence of CHF.

Diltiazem: In general, there has been less experience with diltiazem than nifedipine in CHF. Walsh et al[19] administered intravenous diltiazem to 8 patients with New York Heart Association (NYHA) class III or IV CHF during cardiac catheterization. The mean ejection fraction was 26% with an initial end-diastolic pressure of 29 mm Hg. There was improvement in both cardiac index and lowering of the wedge pressure. However, 1 patient developed bradycardia with hypotension. Other investigators have noted an increase in cardiac index during diltiazem treatment without lowering of the LV filling pressure.[13]

In our own institution, intravenous diltiazem has been administered to patients with acute CHF accompanied by rapid atrial fibrillation or flutter. In these patients with pulmonary edema, the antiarrhythmic effect of intravenous diltiazem was paramount, with reduction of heart rate from 144 to 114 beats/min. Neither cardiac index nor pulmonary artery wedge pressure changed significantly with diltiazem, despite a significant lowering of systemic vascular resistance.

There have been several long-term studies involving diltiazem with divergent results. The most disturbing data about diltiazem in patients with

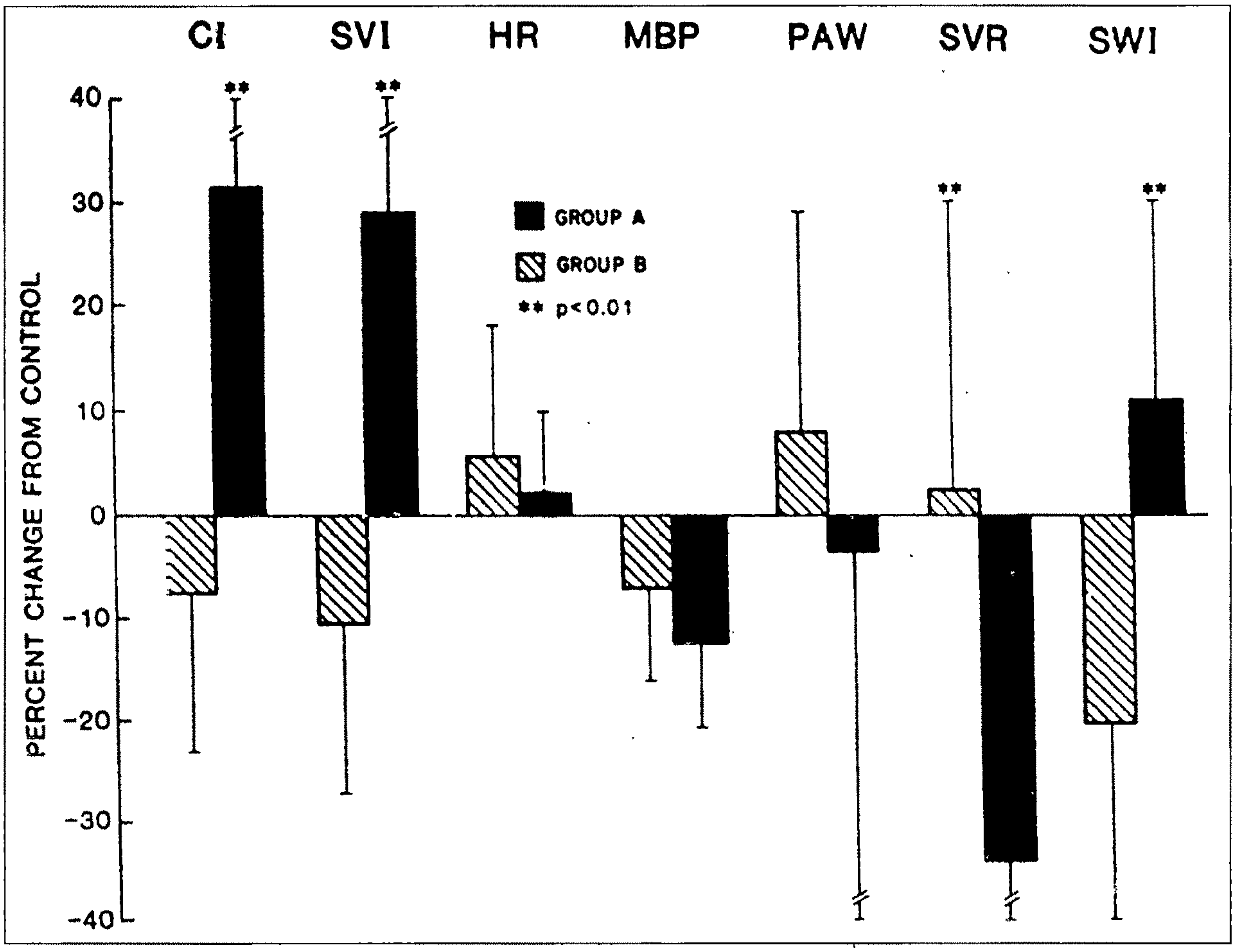

FIGURE 2. Data from patients with severe congestive heart failure (mean ejection fraction 17%) who were given nifedipine. Most patients improved (group A), but approximately one third (group B) showed hemodynamic deterioration. CI = cardiac index; HR = heart rate; MBP = mean blood pressure; PAW = pulmonary artery wedge pressure; SVI = stroke volume index; SVR = systemic vascular resistance; SWI = stroke work index. Reprinted with permission from *Am J Cardiol.*[14]

CHF come from the Multicenter Diltiazem Post-Infarction Trial.[20] In this randomized, double-blind study involving almost 2,500 patients, there was a 150% increase in mortality in those patients who had pulmonary vascular congestion during their infarction. Figulla et al[21] reported strikingly different results in patients with idiopathic dilated cardiomyopathy. In this randomized although unblinded study, oral diltiazem was administered for several years. The mean ejection fraction for this group was 34%. However, about 40% of the patients were in NYHA class I or II. Mean survival time in the control group was 29 months, whereas there were no deaths in the group given diltiazem (Figure 3). There was also an increase in ejection fraction in the patients given diltiazem.

How can these divergent results be explained? Calcium antagonists stimulate the renin–angiotensin system and may thus potentiate detrimental neurohumoral changes that follow an acute reduction in LV function, i.e., myocardial infarction.[9] Since blocking the renin–angiotensin system after an anterior infarction appears to be beneficial,[22] stimulating this system with calcium channel blockade may be counterproductive. The deaths in the diltiazem postinfarction trial did not occur immediately after institution of the therapy, which most probably would be the case if the negative inotropic action of diltiazem were the mechanism of action. The delay in mortality is more consistent with an activation of the sympathetic or renin–angiotensin system. Furthermore, calcium antagonists may prevent ventricular remodeling or interfere with compensatory hypertrophy of the remaining normal myocardium after the infarction.

Still unclear is why a calcium antagonist might be useful in idiopathic dilated cardiomyopathy. Several investigators have speculated that this disease may have an ischemic component.[21] Angina-like chest pain, abnormal thallium treadmill tests, and decreased coronary reserve in these patients support this point of view.[23,24] In an animal model (Syrian hamster) of an inherited form of cardiomyopathy, microvascular spasm has been improved by verapamil.[25] What relevance this model has to the human is not known.

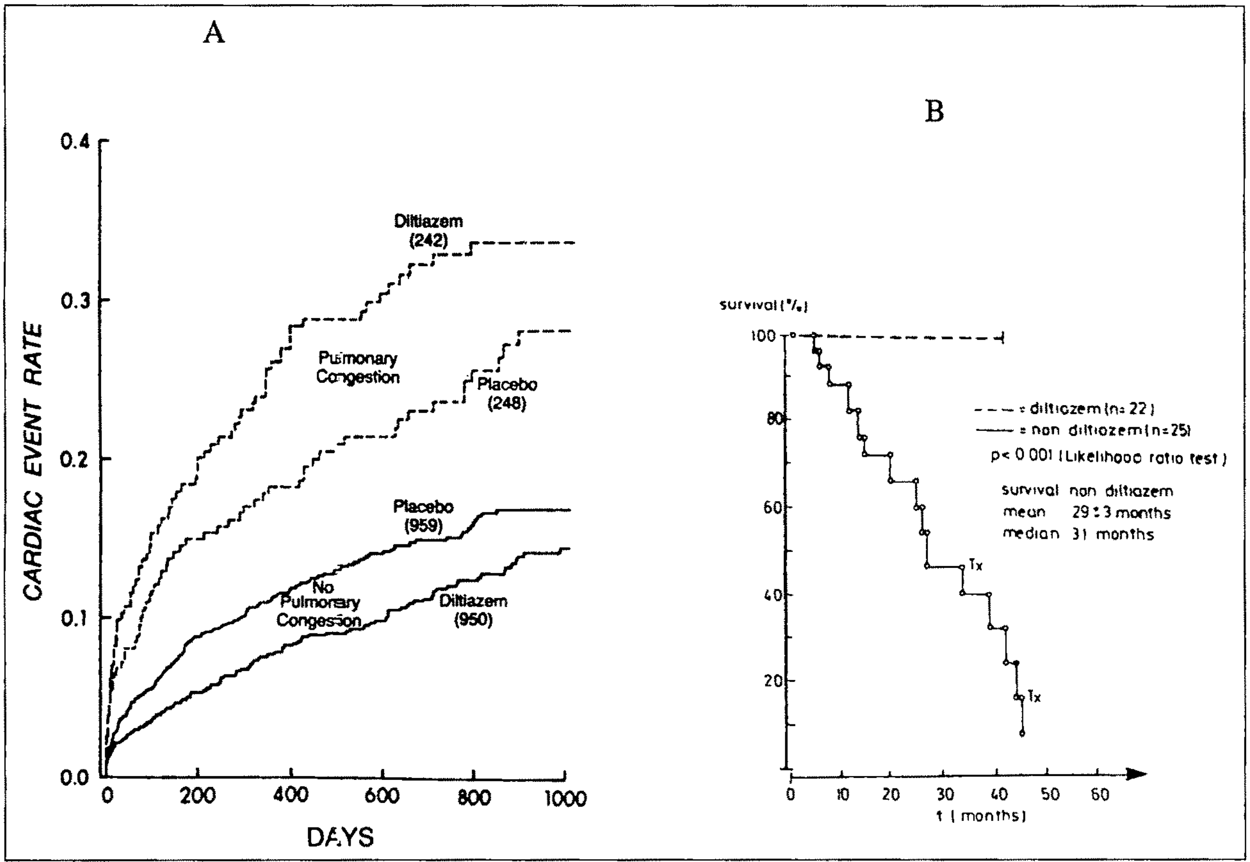

FIGURE 3. *Left:* Results from the Multicenter Diltiazem Postinfarction Trial. In patients with pulmonary congestion following an infarction, there was a significant increase in mortality when diltiazem was added to therapy. Reprinted with permission from *N Engl J Med.*[22] *Right:* Figulla et al[21] noted a striking reduction in mortality in patients with idiopathic dilated cardiomyopathy who were given diltiazem. Reprinted with permission from *J Am Coll Cardiol.*[21]

DIASTOLIC DYSFUNCTION

So far, this report has dealt exclusively with systolic abnormalities of the left ventricle. However, calcium antagonists effect relaxation and thus can influence diastolic filling. There have been numerous reports describing improved relaxation and filling seen with verapamil, nifedipine, and diltiazem in hypertrophic cardiomyopathy.[26–28] Verapamil has also been shown to improve these parameters in nonobstructive forms of LV hypertrophy.[29] In an intriguing recent report by Setaro et al,[30] verapamil was given to patients with radiologic and clinical evidence of CHF but with normal systolic function. All patients had LV hypertrophy and none had evidence of coronary disease. Verapamil brought about a modest improvement in exercise performance and ameliorated roentgenographic evidence of CHF. Since approximately one-quarter of patients with CHF have predominantly diastolic ventricular impairment, the calcium antagonists may have an important role in these patients.

DISCUSSION

What is the role of calcium antagonists in patients with LV dysfunction? The calcium antagonists, although potent vasodilators like prazosin and minoxidil, are not useful as primary treatment in patients with CHF. They do produce short-term hemodynamic improvement, but can also cause clinical deterioration in older patients and those with more severe ventricular impairment. Verapamil can occasionally be used in patients with significant LV dysfunction, yet it may cause clinical deterioration and thus should be avoided in patients with ejection fraction <35%.

The calcium antagonists may have a role in treating coexistent medical problems in patients with LV dysfunction. Angina pectoris is a common problem in patients with LV dysfunction. At the present time there are very few data concerning the safety of calcium antagonists in this large group of patients. In a retrospective review of 3,081 patients given nifedipine for angina, 233 were diagnosed as having CHF.[31] Discontinuance of nifedipine for adverse events in this cohort of patients was not more common than in the non-CHF group. A randomized trial of calcium antagonists in patients with angina pectoris and LV dysfunction secondary to remote myocardial infarctions is needed to address the safety and efficacy of these agents for this group.

Short-term use of calcium antagonists for myocardial ischemia or rapid atrial fibrillation is probably safe when LV dysfunction, even overt CHF, is present. Diltiazem should not be used following an acute myocardial infarction in patients with pulmonary vascular congestion. The calcium antagonists appear to have a role in patients with diastolic dysfunction of diverse etiologies.

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The Role of Coronary Angioplasty in the Management of Unstable Angina Pectoris

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Using percutaneous transluminal coronary angioplasty (PTCA) as primary therapy for unstable angina is quite common. Unstable angina appears to be the indication for the procedure in approximately one third of all PTCA attempts. Considering the unstable nature of the placque in this type of angina, and the increased risk of abrupt occlusion due to frequent intraluminal thrombus, the generally reported rate of success, approximately 85%, is highly respectable. The evidence supporting a period of pretreatment with aspirin and heparin is strong. Less certain is the value of concomitantly administering plasminogen activators. Pending data should produce important further guidelines for effective therapy. Major trials, some using fibrinolytics as well as taking an overall aggressive, interventional approach (like that taken by UNSA, TIMI-III, and others), are reaching the recruitment-completion and promulgation stages.

(Am J Cardiol 1991;68:58C–60C)

Percutaneous transluminal coronary angioplasty (PTCA) was developed and initially advocated as a treatment alternative for carefully selected patients with stable angina pectoris.[1] During the brief decade since angioplasty's introduction, however, the syndrome of unstable angina (using its broadest definition) has emerged as perhaps the leading current indication for using the procedure. As with the other commonly used treatments for the unstable angina patient (β blockers and calcium antagonists), the decision to apply PTCA is based more on logic, judgment, and the knowledge of good outcome in sequential patients, and less on effectiveness proved by clinical trials.

PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY

Frequency of PTCA treatment of unstable angina: Unstable angina is probably the leading diagnostic indication for angioplasty as currently practiced. As early as the time of the first National Heart, Lung, and Blood Institute registry,[2] this syndrome accounted for approximately 40% of all such procedures attempted. Just a few years later, as compiled by the second registry,[3] unstable angina patients accounted for 49% of all angioplasties. Obviously, the representation of such patients among overall PTCA candidates in individual institutions differs greatly, because of hospital location, for example, and probably even more so because of the nature of each practice, i.e., direct admission versus carefully selected referral populations. In published reports, the fraction of unstable angina patients in PTCA series varies widely, from 20% to 70%.

Results of PTCA therapy for unstable angina: Even though angioplasty is extensively used to treat unstable angina, the immediate and long-term results are not as favorable for this syndrome as those expected for chronic stable angina. The presumptive explanation is the presence of intracoronary thrombus with its attendant augmented risk of abrupt total occlusion of the instrumented

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artery after the procedure. In one of several earlier publications on the subject, Mabin et al[4] described the highest reported abrupt occlusion rate, 73%, in a small series of 15 patients in whom pre-PTCA thrombus was angiographically evident. That finding was in contrast to an occlusion rate of only 8% for 223 patients with no evident clot. Even the latter incidence is substantial, but not altogether surprising, for, as has been established, intracoronary clots are far more common with unstable angina than can be distinguished angiographically. The frequency of clot occurrence with the syndrome has been estimated to approach 100% when diagnostic techniques such as angioscopy or biochemical sampling for clot markers (for example, thrombin–antithrombin III complexes) are used.[5,6]

The overall risk of PTCA-associated abrupt occlusion for patients with unstable angina is clearly less than the 73% cited above, but equally clear is that their risk is significantly augmented compared with the risk for patients with chronic stable angina. In a substantial series from the Netherlands, Kemp et al[7] compared PTCA outcome for 334 unstable and 507 stable patients. The acute myocardial infarction incidence (presumably secondary to abrupt total occlusion) was 9% for the unstable angina cohort and 4% for the stable cohort ($p < 0.01$). The angioplasty was initially successful for 83% of the unstable patients and for 87% of the stable patients.

Even after successful PTCA for unstable angina, recently published information suggests that the long-term restenosis rate is nevertheless higher for such patients. Frid et al[8] report that the 6-month restenosis incidence among various subcategories of unstable patients is between 40% and 60%, compared with a 20–30% rate for stable patients.

Ancillary therapy: Understanding that a pre-PTCA intraluminal clot has a negative impact on outcome has predictably led to the testing of strategies using preangioplasty heparin, plasminogen activators, and other hematologically active agents. (Virtually all PTCA candidates, stable and unstable, routinely receive aspirin for preprocedure platelet inhibition.)

Several groups of investigators have evaluated the protective value of a course of intravenous heparin before PTCA (Table I). Laskey et al[9] reported a high success rate, 91%, and no abrupt closures among patients administered heparin before undergoing PTCA for unstable angina. For patients who were not pretreated, the success rate was 81%, with 2% abrupt closure. Similar advantages of a preangioplasty course of heparin anticoagulation therapy have been reported by Hettleman et al,[10] Pow,[11] and others. The association of clot with unstable angina leads to another logical therapeutic intervention, the use of plasminogen activators. Reports of small trials of lytic therapy have been appearing periodically, including several in which these agents were evaluated as adjuncts to or in preparation for angioplasty. Topol et al[12] reported on the course of a small number of patients (n=40) randomly assigned to receive tissue plasminogen activator or placebo after hospital admission for unstable angina. A favorable trend toward reduced culprit-vessel stenosis and an uncomplicated PTCA procedure was observed for the tissue plasminogen group, but the small sample size of the study precludes a definite endorsement.

TABLE I Effect of Heparin on Percutaneous Transluminal Coronary Angioplasty for Unstable Angina

Investigators	No.	Initial Success	Abrupt Closure
Pow[11]			
Heparin	41	—	0%
No Heparin	69	—	10%
Laskey et al[9]			
Heparin	167	91%	2%
No Heparin	139	81%	8%
Hettleman et al[10]			
Heparin	62	95%	2%
No Heparin	126	78%	10%

More experience has accrued using systemic fibrinolytics, including 3 very recent preliminary reports on urokinase therapy and angioplasty for unstable angina.[13–15] All 3 studies reported improved PTCA outcome when a lytic drug was administered first.

Timing strategies: If patients undergo PTCA without delay—i.e., soon after admission for unstable angina—the procedure can be performed with respectable success and complication rates, particularly under "cover" of aspirin and heparin. Moreover, an interim period, during which patients receive antiplatelet, anticoagulant, and possible lytic therapy, apparently facilitates PTCA outcome. The periods selected, particularly for continuous intravenous heparin infusion before PTCA, range from 1 day to 1 week.[9–11] It is not at all clear, on the basis of published studies, that longer waiting periods and anticoagulation treatment intervals (for example, a week) are superior to briefer periods (1–4 days).

Current recommendations: The literature appears currently to support initially managing unstable angina with multiple pharmaceuticals, relying on nitrates, aspirin, heparin, and possibly calcium antagonists. It is not clear whether angiography, and possibly PTCA, is best put off for only 1–2 days of medical therapy or for a week. Apparently, however—analogous to observations of patients receiving thrombolytics for acute infarction—the longer hematologically active drugs are administered, the smaller will be the fraction of patients with a residual high-grade stenosis who will, presumably, require angioplasty.

Data pending: Many of the unanswered questions specifically regarding the use of plasminogen activators and PTCA to treat unstable angina are currently under intensive investigation. The Thrombolysis in Myocardial Infarction (TIMI) study group, sponsored by the National Heart, Lung, and Blood Institute, is approaching the completion and promulgation point in a series of studies related to managing unstable angina. In TIMI-IIIA, angiographic and clinical end points will be compared between patients who receive tissue plasminogen activator and those who receive placebo after an initial quantifying coronary angiogram. In TIMI-IIIB, the clinical outcomes of patients who randomly receive the plasminogen activator or its placebo will be compared. In addition, patients randomly assigned to an aggressive treatment plan—i.e., early angiography-guided treatment (with extensive use of PTCA or coronary artery bypass grafting)—will be compared with subjects following a conservative plan, in which interventions will be undertaken only if thresholds for early recurrent ischemia are exceeded.

In conclusion, the role of PTCA in the management of unstable angina is currently highly visible and PTCA appears to produce a generally favorable outcome. Pharmacologic adjunctive therapy may increase its effectiveness, and trials designed to define better an optimal overall therapeutic strategy are under way.

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Initial Treatment of Patients with Acute Ischemic Heart Disease Hospitalized in a Community Hospital

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During the 1980s, tremendous advances occurred in understanding the pathophysiology of ischemic heart disease. Numerous clinical trials were performed to help clinicians formulate treatment plans and diagnostic schemes to care for patients with coronary artery disease. To see how these studies affect the evaluation and treatment of patients with acute coronary syndromes today, we reviewed the hospital records of patients admitted to our community hospital during September 1990. We found that such patients generally have a good short-term prognosis. Most can be stabilized using modern medical means, and in-hospital mortality is low. Antithrombotic and antianginal therapies are used liberally. Thrombolytic therapy is administered commonly, even to elderly patients. Invasive and noninvasive diagnostic testing procedures are both used frequently, and most acute myocardial infarction and unstable angina patients undergo revascularization.

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The 1980s brought tremendous advances in our understanding of the pathophysiology of acute ischemic heart disease syndromes and of the role of coronary vasomotion, acute changes in the atherosclerotic plaque, thrombus and platelet activation, and arachidonic acid metabolites in patients with acute ischemic syndromes. Numerous clinical trials, performed mostly at large university-affiliated medical centers, have applied this knowledge of precipitating factors and pathophysiology to patient treatment and have better defined the uses of coronary revascularization and antithrombotic and antiischemic therapy.

How the knowledge of etiology and treatment has translated to the care of patients with definite or suspected acute ischemic heart disease admitted as emergency cases to a community hospital is unclear, however. Thus, we reviewed the treatment, evaluation, and disposition of patients with diagnoses of acute myocardial infarction, unstable angina, and chest pain of unclear etiology who were admitted to our hospital during a recent 1-month period.

METHODS

Patient selection: Charts of all patients admitted to our medical center during September 1990 were evaluated. The medical center is a 293-bed, not-for-profit, community hospital with 28 intensive care and 56 additional monitored step-down unit beds. The emergency room is very active. Patient treatment was directed by the admitting physician. If the primary physician was an internist or a family physician, a cardiologist was consulted for patients admitted to a critical care unit. The charts of patients with an admission diagnosis of known or suspected acute ischemic heart disease syndromes—e.g., acute myocardial infarction, unstable angina, chest pain, and sudden death—were retrospectively reviewed. (The charts of patients who died suddenly but did not have an acute infarction were not included in the study.)

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TABLE I Acute Coronary Syndromes, Patients Admitted September 1990

Diagnosis	Total No. of Pts.	Direct Admission	Transfers
Acute myocardial infarction	25	15	10
Unstable angina	81	71	10
Chest pain of unclear etiology	36	35	1
Total	142	121	21

TABLE II Patient Demographics

Diagnosis	Total No. of Pts.	Male/Female	Age (yrs) (Mean ± SD)
Acute myocardial infarction	25	15/10	60 ± 11
Unstable angina	81	49/32	57 ± 13
Chest pain of unclear etiology	36	15/21	64 ± 12
Total	142	79/63	

SD = standard deviation.

Differentiating between unstable angina and chest pain is subjective, but, in general, patients with histories clearly typical of ischemic chest pain, with known coronary disease, or with reversible electrocardiographic changes during chest pain, were usually diagnosed as having unstable angina. Patients with less typical symptoms and normal electrocardiograms but with suspected ischemic heart disease requiring hospitalization were usually diagnosed as having chest pain of unclear etiology. When it was clear, the admission diagnosis of the attending physician was used; if the diagnosis was in question, the opinion of the consulting cardiologist was used. Patients with coronary artery disease who were admitted for elective catheterization, aortocoronary bypass (ACB) surgery, or percutaneous transluminal coronary angioplasty (PTCA) were excluded, as were patients with valvular heart disease or congestive heart failure without acute infarction or unstable angina.

The patients' charts were reviewed for the following: age, gender, admission and discharge diagnoses, medical regimens before and during hospitalization, diagnostic testing performed, and whether the patient had undergone PTCA or ACB surgery. Diagnostic testing included combined 2-dimensional echocardiography and color-flow Doppler, thallium exercise stress testing (stress testing without perfusion imaging is rarely used), and diagnostic catheterization. Finally, the patients' hospital outcome and disposition were evaluated.

In all, 142 patients with acute coronary syndromes were admitted to the medical center (Table I). Most patients (85%) were directly admitted, and a minority (15%) were transferred from hospitals in neighboring counties for diagnostic catheterization and possible revascularization. In general, transferred patients were more likely to have had an acute myocardial infarction or complicated unstable angina and least likely to have chest pain of unclear etiology. More patients with acute infarction or unstable angina were men, whereas more women were admitted with chest pains (Table II). Patients tended to be elderly, but ages were similar for the 3 diagnostic categories.

RESULTS

For evaluation purposes, medical treatment was divided into antithrombotic and antianginal categories. Patients referred from other hospitals were, obviously, selected and consistently treated with more medications. Thus, to assess usual drug treatment, only the regimens of the 121 directly admitted patients were considered.

Thrombolytic therapy (Table III), exclusively tissue plasminogen activator, was used for 6 patients, including 33% of those with acute myocardial infarction. One unstable angina patient with transient anterior ST-segment elevation during angina that was refractory to antianginal treatment was given lytic therapy; enzymes never increased and the ST segments returned to baseline. The age range of the patients receiving thrombolytic therapy was 41–73 years. Heparin—usually in full anticoagulant doses to raise the activated partial thromboplastin time (aPTT) to twice normal—was given to most infarction patients, to the "sickest" unstable angina patients, and occasionally to patients with chest pain. Aspirin was given to all infarction patients, to most unstable angina patients, and to a minority of patients with chest pain. More than half of the patients for whom aspirin was prescribed were already taking it when they were admitted. No minor or major episodes of bleeding occurred in any patients.

Nitrates (Table IV) remain a cornerstone of treatment. Two thirds of the acute infarction patients and one-third of the unstable angina patients were administered intravenous nitroglycerin. Nearly all infarction patients and 65% of those with unstable angina were given long-acting nitrates. Intravenous nitroglycerin was infrequently used for patients with chest pain, but long-acting nitrates were given to 57%. Many patients in all groups (42%) were taking nitrates before hospital admission.

The β blockers used (Table V) are grouped together because, in our opinion, they were similar,

TABLE III Antithrombotic Therapy, Direct-Admission Patients

Diagnosis	Total No. of Pts.	Lytic	Heparin Intravenous	Heparin Subcutaneous	Heparin Total	Aspirin Prior	Aspirin New	Aspirin Total
Acute myocardial infarction	15	5	11	1	12	3	12	15
Unstable angina	71	1	17	15	32	35	26	61
Chest pain of unclear etiology	35	0	4	1	5	8	3	11
Total	121	6	32	17	49	46	41	87

since none with intrinsic sympathomimetic activity was prescribed. These drugs were prescribed for 27% of patients with acute myocardial infarction and for 52% of patients with unstable angina; they were only infrequently prescribed for patients with chest pain of unclear etiology.

The calcium antagonists (Table VI) are listed separately because of their different intrinsic properties. Only one calcium antagonist was used at a time for any patient. Occasionally, one agent was changed for another. Many of the patients were taking a calcium antagonist when admitted or one was added during admission. Diltiazem and nifedipine were most commonly (and almost equally) used, with a small minority of patients prescribed verapamil and only 2 taking nicardipine. Often, the sustained-release preparations were used, especially as discharge prescriptions. Most patients with acute infarction (87%) or unstable angina (77%) either were taking a calcium antagonist on admission or one was added; thus, these were the most popular antianginal medications. Patients with chest pain of unclear etiology were also frequently treated with a calcium antagonist (71%).

Combination therapy (Table VII) was often used, particularly for patients with acute myocardial infarction or unstable angina. The most commonly prescribed combination was either a calcium antagonist plus a β blocker or a calcium antagonist plus nitrates. Occasionally all 3 types of antianginal drugs were used together.

Ultrasound examination (Table VIII) was performed for 72% of the patients with acute myocardial infarction, for 47% of the patients with unstable angina, and for 36% of the patients with chest pain. Thallium stress testing (Table IX) was used for approximately one fourth of patients with infarction and for about half of the patients with unstable angina or chest pain.

Most patients with infarction (72%) or unstable angina (79%) and about one third of those with chest pain underwent diagnostic catheterization (Tables X and XI). Acute myocardial infarction patients who received thrombolytic therapy were all advised by their admitting physician to undergo catheterization (1 declined), and catheterization was performed electively for the remaining patients 3–5 days after admission. Two infarction patients had emergency catheterization: One had waxing and waning angina for more than 12 hours and the other was in cardiogenic shock. Some patients who were not catheterized had had previous catheterization studies.

As expected, the finding of no severe (≥50% diameter reduction) coronary artery disease was more common among patients with chest pain (38%) than among patients with unstable angina (22%) or acute myocardial infarction (6%). Single-vessel disease was found in 44% of infarction patients, in 22% of unstable angina patients, and in 24% of patients with chest pain, whereas multivessel disease was found in 50%, 56%, and 38%, respectively. Prior ACB surgery had been performed in 24% of the patients.

Revascularization was frequently applied as definite therapy (Table XII). Of patients with acute myocardial infarction, 56% (14) underwent PTCA (7) or ACB (7) before discharge; 9 patients were discharged on a regimen of medications alone. In the unstable angina group, revascularization was applied for 59%, with most (78%) of these patients

TABLE IV Nitrate Therapy, Direct Admission Patients

Diagnosis	Total No. of Pts.	Long-Acting Nitrates Prior	Long-Acting Nitrates New	Long-Acting Nitrates Total	Intravenous Nitroglycerin
Acute myocardial infarction	15	8	6	14	10
Unstable angina	71	30	16	46	24
Chest pain of unclear etiology	35	13	7	20	3
Total	121	51	29	80	37

TABLE V Beta-Blocker Therapy, Direct Admission Patients

Diagnosis	Total No. of Pts.	β Blocker Prior	β Blocker New	β Blocker Total
Acute myocardial infarction	15	1	3	4
Unstable angina	71	22	15	37
Chest pain of unclear etiology	35	2	0	2
Total	121	25	18	43

TABLE VI Calcium Antagonist Therapy, Direct-Admission Patients

Diagnosis	Total No. of Pts.	Diltiazem			Nicardipine			Nifedipine			Verapamil		
		Prior	New	Total	Prior	New	Total	Prior	New	Total	Prior	New	Total
Acute myocardial infarction	15	2	2	4	1	0	1	5	2	7	0	1	1
Unstable angina	71	18	10	28	0	1	1	14	10	24	2	0	2
Chest pain of unclear etiology	35	7	10	17	0	0	0	4	3	7	1	0	1
Total	121	27	22	49	1	1	2	23	15	38	3	1	4

TABLE VII Combination Therapy, Direct Admission Patients

Diagnosis	Total No. of Pts.	Calcium Antagonist plus β Blocker	Nitroglycerin plus β Blocker	Nitroglycerin plus Calcium Antagonist	All 3	Single Agent	None
Acute myocardial infarction	15	2	2	10	0	1	0
Unstable angina	71	24	2	28	11	5	1
Chest pain of unclear etiology	35	1	1	8	0	18	7
Total	121	27	5	46	11	24	8

receiving PTCA; and 33 patients (41%) were prescribed medications alone when discharged. Of the patients with an initial diagnosis of chest pain of unclear etiology, the vast majority (94%) were discharged on a regimen of antianginal medications of some type, and only 2 (6%) had revascularization, both treated with PTCA.

Of patients who were revascularized, 73% underwent PTCA and 27% had ACB surgery. PTCA was frequently applied to both multiple-vessel (53%) and single-vessel disease (47%) (Table XIII), and it was successful (final result <50%, no acute myocardial infarction, bypass surgery, or recurrent in-hospital angina) for all these patients. All bypass patients had multivessel disease. Left ventricular ejection fraction was reduced in many patients who underwent either PTCA (46±13%) or ACB (44±12%). PTCA was applied as an emergency measure for 1 patient with an evolving acute myocardial infarction who had waxing and waning angina for more than 12 hours before admission. ACB surgery was performed urgently (4 days after admission) for another patient who was in cardiogenic shock with an evolving inferior-posterior infarction. Emergency catheterization showed multivessel disease, an open infarct-related dominant circumflex artery, and an occluded anterior descending artery. Inserting an intraaortic balloon pump stabilized the patient until bypass surgery was performed.

TABLE VIII Patients, Direct Admissions and Transfers, Who Underwent Echocardiographic and Doppler Ultrasound Testing

Diagnosis	Total No. of Pts.	Tested	%
Acute myocardial infarction	25	18	72
Unstable angina	81	38	47
Chest pain of unclear etiology	36	13	36
Total	142	69	49

The in-hospital prognosis was generally good (Table XII). Only 3 patients died. One was a 67-year-old woman with acute myocardial infarction complicated by reinfarction, heart failure, and recurrent ventricular tachycardia. She had inoperable, undilatable disease and poor ventricular function. The second was an 84-year-old woman with an anterior infarction who died from pump failure; she had not been catheterized. The third patient was a 73-year-old woman with unstable angina refractory to medical therapy; angiography showed right coronary occlusion and severe proximal anterior descending stenosis adjacent to the left main

TABLE IX Patients, Direct Admissions and Transfers, Who Underwent Thallium Stress Testing

Diagnosis	Total No. of Pts.	Tested	%
Acute myocardial infarction	25	6	24
Unstable angina	81	35	43
Chest pain of unclear etiology	36	18	50
Total	142	59	42

TABLE X Direct-Admission and Transfer Patients Who Underwent Diagnostic Catheterization

Diagnosis	Total No. of Pts.	Tested	%
Acute myocardial infarction	25	18	72
Unstable angina	81	64	79
Chest pain of unclear etiology	36	13	36
Total	142	95	67

TABLE XI Coronary Angiographic Findings: Number of Vessels with ≥50% Diameter Stenosis, All Patients

Diagnosis	No. of Pts. Catheterized	Vessel Disease				Prior Aortocoronary Bypass
		0	1	2	≥3	
Acute myocardial infarction	18	1	8	5	4	2
Unstable angina	64	14	14	24	12	12
Chest pain of unclear etiology	13	5	3	4	1	2

artery. She had bypass surgery, but died postoperatively. Thus, hospital mortality was 8% for acute myocardial infarction, 1% for unstable angina, and 0% for chest pain patients.

DISCUSSION

Today, patients admitted to the hospital with known or suspected acute ischemic heart disease have a generally good short-term prognosis. The knowledge gained from basic research and clinical trials is applied in practice, and almost all patients can be stabilized. Both antithrombotic and antianginal therapies are used liberally. Prudent but frequent use of both noninvasive and invasive diagnostic testing leads to revascularization for the majority of patients with acute myocardial infarction and unstable angina.

Our medical center is located in a retirement area and most of our patients are elderly, usually > 65 years of age. Nevertheless, in-hospital mortality was low (8% acute myocardial infarction, 1% unstable angina, and 0% chest pain). (All patients who died were women, aged 67, 73, and 84 years.) We attribute this low mortality to aggressive medical treatment to initially stabilize the patient, frequent use of revascularization, and a low procedural complication rate.

PTCA was more commonly used than ACB (2.8 to 1). None of the patients referred for bypass surgery could be completely revascularized with PTCA and all had multivessel disease. Left ventricular ejection fraction was reduced in both groups. All patients with single-vessel disease who were referred for revascularization had PTCA.

Medical therapy stabilized almost all patients and was the definitive therapy for many. No patient was discharged with continuing in-hospital ischemic chest pain. Therapy designed to dissolve, diminish, or prevent thrombosis was administered to almost all infarction and unstable angina patients, and to chest pain patients when suspicion of ischemic heart disease was highest. Thrombolytic therapy was used for one third of the direct-admission patients with acute myocardial infarction. Of the 10 direct-admission infarction patients who did not receive thrombolytic therapy, only 1 met the generally established criteria for lytic therapy; 7 did not show significant ST-segment elevation on their admission electrocardiogram, and each developed a non-Q-wave infarction. Two patients did have significant ST-segment elevation but presented more than 6 hours after the onset of symptoms: 1 patient whose waxing and waning angina was ongoing despite intravenous nitroglycerin therapy received emergency direct PTCA; the other was managed conservatively. The last acute myocardial infarction patient was in cardiogenic shock and had waxing and waning angina with variable but extensive ST elevation; thrombolytic therapy was considered but emergency catheterization stabilized the patient with an intraaortic balloon pump support. ACB surgery was performed for multivessel disease. Thus, in 1990, thrombolytic therapy was administered liberally even to elderly patients.

Full-dose heparin anticoagulation therapy was administered to most acute myocardial patients and to many unstable angina patients. Low-dose heparin was used in most other patients who were on bed rest. During hospitalization and at discharge, all infarction patients and 86% of unstable angina patients were prescribed aspirin; usually enteric coated, 325 mg/day. Thrombolytic therapy prevented an acute myocardial infarction in an unstable angina patient who had recurrent angina

TABLE XII Revascularization Versus Medical Therapy, All Patients

Diagnosis	Total No. of Pts.	Catheterization	Percutaneous Trans uminal Coronary Angioplasty	Aortocoronary Bypass	Catheterization plus Medical Therapy/Medical Therapy Only
Acute myocardial infarction	25	18	7	7	4/7*
Unstable angina	81	64	38	10*	16/17
Chest pain of unclear etiology	36	13	2	0	11/23
Total	142	95 (67%)	47 (33%)	17 (12%)	78 (55%)

*2 acute infarction patients and 1 unstable angina patient died.

TABLE XIII Revascularization and Percutaneous Transluminal Coronary Angioplasty, All Patients

Diagnosis	Total No. of Pts.	No. Vessels Revascularized			
		4	3	2	1
Acute myocardial infarction	7	1	1	1	4
Unstable angina	38	2	5	13	18
Chest pain of unclear etiology	2	0	1	1	0
Total	47	3	7	15	22

and ST-segment elevation despite heparin, aspirin, and intravenous nitroglycerin therapy. No bleeding complications occurred in any patient who received thrombolytic therapy, heparin, or aspirin. Of antianginal medications, the calcium antagonists were used most frequently and the percentage of patients treated was surprisingly high (77%). Long-acting nitrates (66%) and β blockers (36%) were commonly used as well. Despite the numerous studies documenting the cardioprotective effects of the β blockers, their use for acute myocardial infarction and unstable angina was relatively low (26% and 52%, respectively).

When discharged from the hospital, only 7 patients who were not revascularized—all of whom had been admitted with chest pain of unclear etiology—were not on a regimen of antianginal medication. Several patients with no severe coronary disease and negative ergonovine stimulation tests at catheterization, and other patients with negative thallium stress tests, were discharged on a regimen of antianginal medication—perhaps coronary spasm or the syndrome of angina and normal epicardial coronary arteries (so-called microvascular angina) were still suspected. Most patients who were continued on medical therapy alone were prescribed combinations of antianginal medications. For those who had undergone PTCA or bypass surgery, medication dosages were usually decreased but only occasionally discontinued before discharge. The results of several cooperative trials suggest that patients with acute myocardial infarction who receive thrombolytic therapy can often be managed conservatively. Four of the 5 direct-admission infarction patients in our study who received thrombolytic therapy underwent diagnostic catheterizations; the fifth was advised to, but refused. Of the 5 patients (4 infarction, 1 unstable angina) who received thrombolytic therapy and were catheterized, 3 had PTCA, 1 underwent ACB surgery before discharge, and 1 who had only moderate coronary stenoses was treated medically.

These data suggest that physicians have learned from the major studies of the 1980s, but do not apply the results of all cooperative trials blindly. Antithrombotic therapy is used very commonly in combination with aggressive antianginal therapy, and even elderly patients are often safely treated aggressively. Usually, several medications in each category are used simultaneously. Most patients with acute ischemic heart disease can be stabilized. Although it is not usual in our practice to go straight from the emergency room to the catheterization laboratory, emergency catheterization was an important measure for selected—often the sickest—patients. Noninvasive diagnostic testing and elective catheterization can indicate which patients are most likely to benefit from PTCA or ACB. Revascularization continues to be an important adjunct to medical therapy for most patients. The majority of patients admitted with acute myocardial infarction or unstable angina underwent diagnostic catheterization and revascularization during their hospitalization, whereas most patients with chest pain did not.

These data reflect our practice at a community hospital. They do not necessarily reflect the practice at all hospitals, particularly those choosing to be more conservative. It would be interesting to compare similar data from both urban and rural, university, medical school, and private practices, as well as from both aggressive and conservative practices.

Goals of Thrombolytic Therapy

Neal S. Kleiman, MD

In the past decade, mortality associated with acute myocardial infarction has been reduced to between 5% and 9% in selected groups of patients, largely due to use of early reperfusion. Thrombolytics combined with aggressive mechanical revascularization reduce the likelihood of death both during hospitalization and in the ensuing several years. Overall morbidity is also lessened, although salvage of patients with severe left ventricular dysfunction may make this difficult to demonstrate. Foremost among issues remaining unresolved is the relationship between patency of the infarct vessel and survival. Survival associated with reperfusion is limited primarily to patients with successful reperfusion. Myocardial salvage is more likely in these patients, but the correlation between myocardial salvage and mortality reduction is not determined. Late spontaneous reperfusion occurs in >50% of patients who do not receive a thrombolytic; survival seems to be greater when vessels undergo spontaneous reperfusion. Only a minority of patients can be treated within the first hour after chest pain onset. It is not clear that the time window in which early reperfusion can be accomplished allows benefit to be clinically evident. Resources need to be directed toward agents to augment the rate of lysis and toward improvement of delivery. Mortality is highest in the first 24 hours after thrombolytic administration. Understanding of the underlying mechanisms may promote further reductions in mortality. Intravenous thrombolytic therapy can be given on average 2–3 hours after pain onset. If the myocardial salvage versus time curve is steepest immediately after occlusion, early administration of thrombolytics, such as by paramedics in the field, may be indicated. Greatest time savings are related not to transport, but to evaluation in the emergency room. Application of rapid, sensitive assays to patient selection may extend thrombolytic therapy to a broader group with acute myocardial infarction.

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The past decade has seen tremendous changes in the management of acute myocardial infarction (MI) with mortality reductions between 5% and 9% in selected groups of patients.[1,2] Although this trend is probably multifactorial in nature, it is in large part due to the rapidly increasing use of early reperfusion strategies.[3] The use of thrombolytic agents combined with an aggressive mechanical revascularization strategy in patients with recurrent ischemia and threatened reinfarction has unequivocally reduced the likelihood of death during hospitalization and during the ensuing several years.[1,4–11] In addition, several studies suggest that the overall morbidity associated with acute MI is also lessened,[10–13] although salvage of patients with severe left ventricular (LV) dysfunction may make the latter proposition difficult to demonstrate.[14]

ESTABLISHING VESSEL PATENCY

Several issues still remain to be resolved, however. Foremost is the relationship between patency of the infarct vessel and survival. From the earliest use of lytic therapy, survival benefits were limited primarily to those patients with successful reperfusion.[15–18] These patients were also more likely to have myocardial salvage, manifested by greater preservation of ejection fraction, regional wall motion, and end-systolic volume, [6,19–21] and smaller areas of myocardial scarring measured by radionuclide scintigraphy.[22] However, how closely the degree of myocardial salvage correlates with the extent of mortality reduction is not known. Late spontaneous reperfusion occurs in >50% of patients who do not receive a thrombolytic drug.[23] Even data amassed during the period when patients were rarely, if ever, treated with a reperfusion strategy have demonstrated that survival was better in patients who experienced spontaneous

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reperfusion of infarct vessels compared with those who did not have spontaneous reperfusion.[24]

The lack of definitive proof of the mechanism through which thrombolytic therapy improves the outcome in patients with myocardial infarction has led to several hypotheses. The most tenable is derived from the classic animal experiments of Reimer et al [25] who demonstrated that necrosis of significant portions of myocardium can be prevented by rapid reperfusion of an occluded coronary artery. However, timing of the onset of vascular occlusion and of reperfusion with restoration of adequate antegrade flow is considerably more difficult in human beings. Except for the first Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI) study,[4] most clinical trials have shown a less dramatic relationship between the time of administration of thrombolytic therapy and reduction of mortality than might be predicted from the animal data.[5–7]

Although some of this discrepancy may be due to the difficulty of timing the onset of infarction, examination of the relation between salvage and time of reperfusion offers another potential explanation. This curve is apparently steepest during the first 45 minutes after occlusion,[25] with the slope becoming considerably more shallow during the ensuing few hours. Studies of patients presenting in emergency rooms show that only a minority of those with chest pain can be treated within the first hour after the onset of symptoms.[26,27] Therefore, although common sense indicates that the earlier an infarct vessel is opened, the more the patient benefits, on a practical level it is not clear whether reperfusion can be accomplished within such a window of time and thus allow this benefit to be clinically visible.

Whether this is true has great impact on the way expenditures for direct health care and health care research are directed. Several other mechanisms have been proposed as instrumental in mortality reduction, including electrical stabilization, limitation of expansion of the infarct zone, and provision of collateral flow in patients with multivessel disease.[28] These mechanisms are less dependent on time than is the case with myocardial salvage. Analyses of subgroups of patients in various trials show that infarct vessel patency is a predictor of survival independent of ejection fraction.[29] However, although ejection fraction is the most conveniently measured index of ventricular function, it is a crude measure of myocardial preservation.[30] Thus, it is impossible to separate clearly between the effects of vascular patency and of myocardial salvage for each of the mechanisms proposed. Obviously, research is needed to identify methods to prevent reocclusion once patency is established.[31] However, hastening the onset of lysis is another matter. If, for example, clinical outcome is significantly improved by a modest increase in the speed with which reperfusion occurs after administration of a thrombolytic agent, then efforts need to be directed toward the development of new thrombolytic agents and adjunctive agents designed to augment the rate of lysis. If, on the other hand, clinical outcome is not significantly improved by a moderate increase in the rapidity of lysis, then resources need to be directed toward the development of improved delivery networks and the investigation of adjunctive agents (e.g., vasodilators) for use in the postlytic phase.

To date, however, no study has shown that long-term survival is greater among patients in whom sustained reperfusion occurs earlier. Rather than using the familiar patent versus occluded survival curves, a "family" of curves is needed, each relating survival to reperfusion at a different point in time. The Netherlands Interuniversity Trial graphically illustrates this point. Long-term follow-up showed that survival in patients whose artery was patent at the time of the initial angiogram exceeded that of patients in whom patency was achieved with intracoronary streptokinase, which, in turn, exceeded that of patients with persistent occlusion.[32] However, information from this trial may not tell the whole story, since data were accumulated during a period when reperfusion practices were changing rapidly (i.e., the adoption of intravenous administration) and do not allow for separation of patients with very early spontaneous reperfusion.

This sort of uncertainty surrounds interpretation of data from the recently completed large comparative studies of streptokinase and recombinant tissue-type plasminogen activator (rt-PA).[2,33] Previous studies had shown that early patency rates were greater with second generation or fibrin-specific agents,[34,35] but that rates were likely to equilibrate within the next several hours.[36] It had been hoped that in addition to providing a product-to-product comparison, these trials would answer the critical theoretical question and provide information that would be useful during testing of future regimens. However, interpretation of these trials has been somewhat complicated by recent data indicating that patency rates following the administration of rt-PA, and possibly of streptokinase, are lower than predicted if full-dose intravenous heparin is not used.[37-40] Early reperfusion and patency rates were based on data accumulated in patients who received intravenous heparin, whereas the mortality data were accumulated in patients who also had been randomized to receive either subcutaneous or no heparin. Thus, what is required to answer this question is a trial large enough to examine the mortality issue, in which early coronary angiography is performed in at least a representative sample. Then correlations can be made between early reperfusion rates and clinical outcomes in large population groups. Several trials currently underway are attempting to answer this question.

Another critical issue to be resolved is the tremendous concentration of mortality that occurs during the first 24 hours after thrombolytic therapy is administered. Mortality during the prethrombolytic era was highest during this period and data from several large clinical trials indicate that nearly half the hospital deaths continue to occur during this time frame.[1,2,41] In fact, analysis of data from the GISSI study,[41] and a smaller study[42] indicate that the benefits of thrombolytic therapy are not seen during the first 24 hours. Since mortality appears to be concentrated during the first day after thrombolytic therapy, understanding of the mechanisms responsible might be helpful in achieving a further reduction in mortality. Although data gathered during the prethrombolytic era from a relatively low-risk population suggest that myocardial rupture was responsible for a large proportion of early deaths,[43] the majority of early deaths following thrombolysis appear to be due to pump failure.[44] Most of these deaths occur in patients who have signs of decompensation at the time they present to the hospital.[44] Whether these deaths result from failure to achieve reperfusion, or failure of reperfused myocardium to sustain a cardiac output adequate to support life before some recovery of ventricular function occurs, is not known. Experience with primary angioplasty suggests that a combination of both factors may be operative. An understanding of this mechanism and a means to identify patients at risk for early death might help in deciding which patients need more aggressive mechanical revascularization and access to mechanical support devices.

IMPROVING DELIVERY SYSTEMS

Another critical issue concerns delivery systems for thrombolytic agents. A major advance in thrombolysis occurred when it became clear that it was not necessary to perform coronary angiography before administering the agents. The result: approximately 90 minutes are saved in initiating treatment.[16] Many recent trials demonstrate that intravenous thrombolytic therapy can be administered on the average, 2–3 hours after the onset of pain. However, if the myocardial salvage versus time curve is steepest during the earliest hours after occlusion,[25] then even earlier administration of thrombolytic agents might be indicated. This approach, which involves the administration of thrombolytic agents by paramedics in the field, has been tried in several cities in the United States and Europe, with extremely concordant results. Principal among these results is that up to 90 minutes can be saved if a 12-lead electrocardiogram (ECG) is obtained in the field and lytic therapy is administered to patients with a typical history, no contraindications, and an injury current on the ECG.[45-47] Obviously, concerns about safety arise when the decision-making responsibility is delegated, but preliminary data indicate an extremely high rate of agreement between paramedics and monitoring physicians. Interestingly, the greatest time savings are not related to the transport time itself, but to the evaluation time in the emergency room.[45] This is highlighted by the finding that physicians' perception of time required to begin thrombolytic therapy in the emergency room underestimates the documented time by approximately 60 minutes.[47] To date, the benefit of administering thrombolytic therapy in the field has not been established definitively. However, extrapolation of data from the GISSI study suggests that if expeditious treatment could be implemented on a large scale, the benefits would probably be enormous.

REFINING PATIENT SELECTION CRITERIA

A final critical issue pertains to patient selection. The issues discussed so far apply to only a minority of patients with acute myocardial infarction. In most major trials of thrombolytic therapy only 25% to 30% of patients screened were actually enrolled. This is particularly true for the trials that required specific ECG findings as a requirement for admission. For example, Althouse et al[48] found that 22% of patients presenting in Seattle emergency rooms were eligible for thrombolytic therapy when a relatively standard set of entry criteria (i.e., age ≤ 75 years, pain ≤ 6 hours, injury current on the ECG, and absence of contraindications to fibrinolysis) were used. The most common reason for exclusion was a nondiagnostic ECG, followed by a contraindication to thrombolytic therapy and age > 75 years.[48] In a survey of patients seen in an emergency room in Gothenburg, Sweden, Karlson et al[27] found that if patients with acute ischemic changes or ST-segment elevation on ECG were included, the percentage of patients with eventual confirmation of infarction who were treated increased from 37% to 49%; further extension to those patients with "pathologic" ECGs increased the proportion treated to 67%. However, expanding criteria for use of thrombolytic therapy entails the risk of treating a much larger group of patients, many of whom would not have infarction, at a time when subgroup analyses of patients from 2 large European trials have failed to show benefit in this group,[4,5] and 2 other large trials designed to examine this issue prospectively are not yet completed. The use of rapidly available and sensitive assays, such as isoforms of the creatine kinase MB fraction[49] and serum myoglobin,[50] may prove useful in extending thrombolytic therapy to a broader group of patients with acute MI.

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The Role of Thrombolytic Therapy in Patients with Acute Myocardial Infarction Presenting Later Than Six Hours After the Onset of Symptoms

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Thrombolytic therapy clearly reduces mortality in patients with acute myocardial infarction, especially when initiated within 6 hours of onset of symptoms. Some studies have also suggested that thrombolytic therapy may improve survival even when initiated 6–24 hours after the onset of symptoms by mechanisms other than infarct size limitation, such as reduced expansion, reduced electrical instability, and improved healing of the infarct. However, in view of the possibility that late thrombolytic therapy may also be associated with an increased risk of cardiac rupture, the risk–benefit ratio needs to be more clearly defined. Ongoing randomized trials are expected to clarify the situation in the near future. In the meantime, efforts to initiate reperfusion as soon after the onset of myocardial infarction as possible should continue, since early treatment is still the best treatment.

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Thrombolytic therapy has emerged as a significant therapeutic advance in the management of selected patients with acute evolving myocardial infarction (MI).[1] A number of placebo-controlled clinical trials have clearly demonstrated reduced mortality in patients who receive thrombolytic therapy within 6 hours of onset of symptoms of an acute MI.[1-5] In general, the magnitude of mortality reduction appears to be inversely related to the time delay between the onset of symptoms and initiation of thrombolytic therapy, with the greatest reduction being observed in patients treated within 1 hour of symptom onset.[2,3]

These findings are consistent with several concepts. The first is that following coronary occlusion, myocardial necrosis within the jeopardized zone evolves from subendocardium to subepicardium in a time-dependent course. Completion of transmural necrosis in animal models of coronary occlusion appears to be around 3–6 hours, with inter- and intraspecies variability largely dependent on variations in the extent of collateral flow. The next concept is that reperfusion with thrombolytic therapy reduces mortality, primarily by salvaging ischemic myocardium that has not yet undergone irreversible damage. This limits infarct size and preserves ventricular function.[6-10] In keeping with these concepts, the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI) study, a placebo-controlled randomized trial of thrombolysis in acute MI, showed a gradient for mortality reduction inversely related to the delay between the onset of symptoms and initiation of thrombolytic therapy.[2] In this study, mortality reduction was statistically significant in patients treated within 6 hours of onset of symptoms, with maximum mortality reduction (47%) observed in the subgroup that received thrombolytic therapy within 1 hour of onset of symptoms. Patients receiving treatment 6–12 hours after the

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onset of symptoms did not have a statistically significant reduction in mortality, although the sample size in this trial was not sufficient for adequate statistical power.

A meta-analysis of 33 published clinical trials by Yusuf et al[1] showed that thrombolytic therapy initiated 6–24 hours after the onset of symptoms was also associated with a significant reduction of early mortality. This finding appeared to be at odds with the results of the GISSI trial but was further supported by the large second International Study of Infarct Survival (ISIS-2) study.[3] This trial showed that patients treated with streptokinase 7–24 hours after the onset of symptoms also experienced a significant reduction in mortality (22%) relative to the control group, although the magnitude of mortality reduction was clearly less than that of patients treated within 6 hours of onset of symptoms. Unfortunately, the criteria for inclusion in the ISIS-2 study were relatively loose, requiring simply a clinical suspicion of acute MI regardless of electrocardiographic abnormalities. Thus, it is not clear if all patients receiving treatment late after the onset of symptoms did, in fact, have an acute Q-wave MI. Some of these patients may have had unstable angina, non-Q-wave MI or a stuttering pattern of infarct evolution, making it difficult to interpret the results of late reperfusion.

Although experimental and clinical studies have generally failed to demonstrate a significant improvement in ventricular function when reperfusion is initiated later than 3–6 hours after the onset of infarction, several lines of evidence suggest that thrombolytic therapy may improve survival by additional mechanisms not clearly linked to reduction in infarct size or preservation of resting left ventricular function. In the Western Washington Intracoronary Streptokinase Trial, 1-year survival was substantially higher in patients with an open artery compared with those with a closed artery, despite absence of any difference in infarct size or left ventricular (LV) ejection fraction (measured at 62 days in survivors only) between the 2 groups.[11–13] These results could not be explained entirely on the basis of exclusion of 18 patients who died before LV function or infarct size was determined.

Other randomized studies have also demonstrated that the reduction in mortality with thrombolytic therapy in general is greater than would be expected on the basis of only modest or no improvement in ventricular function.[14–19] This seeming paradox—greater mortality reduction relative to ventricular function preservation—has further raised the possibility that reperfusion may confer additional benefits for survival that are not clearly linked to its effects on resting measurements of global LV function.[20] Although a number of tantalizing interpretations have been offered to explain the survival benefits of arterial patency independent of myocardial salvage and preservation of ventricular function, it should be recognized that a significant number of patients included in randomized trials of thrombolytic therapy have included patients with single- or 2-vessel disease (a relatively low-risk group) and those who have undergone additional revascularization procedures (angioplasty, bypass surgery) that may have independently contributed to the observed benefits.[21] Most thrombolysis studies have examined only the relationship of LV function to mortality; however, right ventricular dysfunction further increases mortality in patients with severely depressed LV function.[22] Conceivably, changes in right ventricular function may account for some of the apparent discrepancies between LV function and survival. Furthermore, the interpretation of ventricular function measurements in survival studies is complicated by the fact that function is frequently measured in survivors only (excluding patients who die before function assessment), whereas the mortality represents the entire study population. Assignment of a zero ejection fraction to nonsurvivors may partially overcome this problem in statistical interpretation.

TABLE I Potential Mechanisms of Mortality Reduction by Thrombolytic Therapy

1. Myocardial salvage, infarct size reduction and ventricular function preservation
2. Reduced ventricular remodeling, infarct expansion, aneurysm formation and rupture
3. Improved infarct healing
4. Reduced vulnerability to ventricular arrhythmias and conduction failure
5. Reduced incidence of thromboembolic complications
6. Open artery serves as a source of collaterals?
7. Concurrent revascularizing interventions (bypass surgery)?

POTENTIAL MECHANISMS OF MORTALITY REDUCTION BY LATE REPERFUSION

Infarct size limitation and function preservation due to an extended time course of evolution of infarction: The time course of evolution of myocardial necrosis may extend beyond the usually accepted time limit of 3–6 hours in certain patients because of significant collateral flow to the postocclusion myocardial zone or intermittent coronary artery occlusion, with cycles of occlusion and reperfusion allowing the infarction to evolve in a stuttering fashion (Table I). This intermittent occlusion-reperfusion cycle may be present in 20–25% of all patients with acute MI.[23] In such patients the time window during which thrombolytic therapy may salvage myocardium and preserve ventricular function, the putative "window of opportunity," is likely to be longer than the traditional 3–6 hours.[24] Inclusion of these patients in late reperfusion trials as well as the uncertainty in clearly defining the exact time of onset acute MI in many patients could, in part, explain the apparent benefits of later reperfusion. Furthermore, limitation of infarct size may not always be reflected in an improvement in resting global or regional function even though functional reserve, demonstrable with provocative testing, is improved. Experimental observations suggest that substantial epicardial preservation may exist without evidence on measurements of resting ventricular function.

Mortality reduction independent of infarct size limitation or preservation of ventricular function—reduction of ventricular remodelling and infarct expansion: After acute MI, progressive thinning and stretching of the infarct zone evolves to localized ventricular expansion, which eventually leads to expansion of the noninfarct zones as well. This remodeling of the ventricle tends to occur most frequently in patients with large transmural anterior infarcts involving the apex.[25] Remodeling is related to infarct transmurality as well as to loading conditions and can occur soon after infarction. It may continue over subsequent weeks, leading to progressive enlargement of the ventricle and increase in end-systolic and end-diastolic volumes. This ventricular expansion may serve as a template for aneurysm formation and cardiac rupture and may be an independent predictor of mortality among patients with depressed LV function.[25–28] Experimental studies and a limited number of clinical studies suggest that spontaneous or therapeutic reperfusion attenuates ventricular remodeling and infarct expansion even in the absence of limitation of infarct size or obvious improvement in ventricular function.[29–34] The mechanisms by which reperfusion attenuates remodeling are not understood, but may include preservation of an epicardial rim of the jeopardized zone; acute changes in afterload due to favorable hemodynamic and rheologic effects of thrombolytic agents; increased infarct stiffness due to contraction bands, the erectile properties of a patent artery or tissue edema and cellular infiltrate; enhanced healing of the reperfused infarct; and better preservation of the intercellular matrix, providing a better scaffolding for the necrotic myocardium.

Reduction in electrical instability and vulnerability to ventricular arrhythmias: Reperfusion is associated with an increase in the frequency of ventricular arrhythmias in the early phase of acute MI, but the frequency and complexity of late ventricular arrhythmias appear to be reduced.[35] Several uncontrolled studies show that reperfusion has a favorable effect on vulnerability to spontaneous as well as inducible ventricular arrhythmias.[36–40] Other studies, however, show no benefit or suggest an increased electrical vulnerability.[41,42] Kersschot et al[38] evaluated 36 patients and observed a significant reduction in the incidence of inducible sustained ventricular tachycardia after acute MI in patients treated with thrombolytic therapy compared with a control group (30% vs 70%; $p < 0.05$). Similarly, Sager et al[40] noted a very low incidence of inducible ventricular tachycardia in a small group of patients receiving thrombolytic therapy compared with a high incidence in those not receiving thrombolytic therapy (8% vs 88%; $p=0.0008$), despite the presence of a ventricular aneurysm and severely depressed LV ejection fraction in both groups. During an average of 11 months of follow-up, 4 patients from the group that did not receive thrombolysis suffered spontaneous ventricular arrhythmias or sudden death; none occurred in patients in the thrombolysis group.[40] Gang et al[43] recently reported a significantly lower incidence of positive late potentials, markers of vulnerability to inducible ventricular tachycardia, in patients with acute MI with a patent coronary artery compared with those with a closed culprit artery (5% vs 23%; $p=0.01$). Other investigators have reported similar results.[44–46] However, all these observations are based on relatively small nonrandomized patient cohorts, and the influence of other confounding variables such as myocardial salvage or improved ventricular function cannot be conclusively excluded. In fact, Kersschot et al[38] reported that the favorable effect of reperfusion on spontaneous as well as inducible ventricular arrhythmias was associated with substantially better LV function in the thrombolysis group.

More recently, Bourke et al[47] reported the results of electrophysiologic studies conducted 6–28 days after an acute MI in 87 patients who were randomized to placebo, aspirin, streptokinase or aspirin plus streptokinase as a part of the ISIS-2 study. Ventricular tachycardia was inducible in 8 of 46 patients who did not receive streptokinase, compared with 0 of 41 patients who received streptokinase ($p=0.005$), despite comparable LV ejection fraction in the two groups.[47] Thus, the favorable effects of reperfusion on electrical instability may result from mechanisms in addition to myocardial salvage, such as better healing of the infarct, better preservation of the architecture and topography of the infarct, washout of chemotoxins, and preservation of a more balanced and homogeneous autonomic innervation.[48,49]

Other potential benefits of an open infarct artery: It has also been suggested that an open artery may serve as a source of collaterals to a neighboring artery: if the second artery becomes occluded, the open artery may limit myocardial damage from a second coronary occlusion. Although this hypothesis is plausible, no evidence as yet directly supports it.[20]

Aggressive antithrombotic therapy as well as thrombolytic therapy reduces the risk of mural thrombosis. Thus, it is expected that thrombolytic therapy may reduce any mortality related to systemic embolic complications irrespective of myocardial salvage.[50]

POTENTIAL RISKS OF LATE THROMBOLYTIC THERAPY

Late thrombolytic therapy may have potentially adverse consequences over and above the well known bleeding complications associated with thrombolytic therapy in general. One concern is the real possibility that if lytic and aggressive antithrombotic therapy is initiated after transmural necrosis is complete, the risk of free wall rupture and cardiac tamponade may also be increased. Furthermore, some patients who present at the hospital several hours or days after MI because of ongoing or recurrent chest pain may actually have postinfarction pericarditis or even impending cardiac rupture. Misinterpretation of these symptoms may expose such patients to serious risks from thrombolytic therapy. Recent observations from a meta-analysis done by Duke University investigators have, in fact, suggested that while the odds of cardiac rupture may be reduced when thrombolytic therapy is given early in the course of MI (≤ 11 hours after onset of symptoms), they are actually increased when thrombolytic therapy is initiated late (> 12 hours after the onset of symptoms).[51] Increased risk of cardiac rupture with late thrombolytic therapy may, however, not apply if primary PTCA is used for reperfusion.

TABLE II Ongoing Clinical Trials of Late Reperfusion in Acute Myocardial Infarction

Trial	Drug	Time Window
TAMI-6	t-PA	6–24 h
LATE	t-PA	6–24 h
EMERA	SK	6–24 h
ISIS-3	t-PA vs SK vs APSAC	0–24 h

APSAC = anisoylated plasminogen streptokinase activator complex; EMERA = Estudio Multicentrico Estreptoquinasa Republica Argentina; ISIS = International Studies of Infarct Survival; LATE = late assessment of thrombolytic efficacy; SK = Streptokinase; TAMI = Thrombolysis and Angioplasty in Myocardial Infarction; t-PA = tissue-type plasminogen activator.

COMMENTS

The data to support routine use of thrombolytic therapy late in the course of acute MI, although promising, are far from conclusive and the possibility of harm must be considered. Before the indications for thrombolytic therapy can be safely expanded to include patients who present late after the onset of symptoms, the risk-to-benefit ratio needs to be defined in more detail.[52] Additional randomized trials are needed clearly to answer this very important question, since liberalization of the window of opportunity would not only considerably expand the pool of patients eligible for thrombolysis, but also may further justify aggressive attempts for mechanical reperfusion in patients who fail intravenous thrombolysis. In the meantime, it appears prudent to reserve late therapy for patients whose clinical and electrocardiographic data suggest intermittent coronary occlusion and a stuttering pattern of infarct evolution and, possibly, in patients who present in cardiogenic shock where the added risks of treatment, if any, may be justified. The relatively high rate of spontaneous late reperfusion in patients receiving only antithrombotic therapy without thrombolytic therapy[53] also raises the question of whether the benefits of late reperfusion in patients who fail early reperfusion with thrombolytic therapy may accrue simply from continuation of antithrombotic therapy, thereby making it unnecessary to engage in rescue percutaneous transluminal coronary angioplasty (PTCA)—a procedure associated with a high mortality and little, if any, improvement in ventricular function.[54] Even if further studies ultimately prove that the therapeutic window of opportunity extends beyond 4–6 hours, those who are treated earliest will continue to benefit the most because thrombolytic efficacy and the magnitude of myocardial salvage achieved are greater with early therapy. Thus, it is imperative that the public, especially individuals at risk for MI, be educated to seek medical attention immediately after the onset of symptoms of prolonged myocardial ischemia. Additionally, physicians in emergency departments and coronary care units must establish treatment protocols for efficient triage and treatment of patients without undue delay. Several ongoing clinical trials will more clearly define the benefits and risks of late reperfusion, especially in patients with clinical evidence of a completed transmural infarct without signs or symptoms of ongoing ischemia or a stuttering evolution of infarction (Table II).

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Introduction

Harvey D. White, MB, ChB, FRACP

Thrombolytic therapy is a major advance in the management of acute myocardial infarction. Major contributions to this area have been made by many groups throughout the world and the rapid progress made over the last few years in understanding and treating this disease has been truly remarkable. Any treatment that reduces mortality by 25% will be difficult to improve on, and indeed this has been the case with thrombolytic therapy. Despite the large number of patients (> 60,000) being randomized in clinical trials, the simplest and cheapest regimen of streptokinase and aspirin has not been surpassed.

However, we must progress and improve on the current "gold standard." In the recent Third International Study of Infarct Survival (ISIS-3) trial, preliminary data indicate that 35-day mortality for all patients, regardless of age, was > 10%, whichever agent—streptokinase, duteplase (tissue plasminogen activator, Burroughs Wellcome), or anistreplase (anisoylated plasminogen-streptokinase activator complex)—was administered. Despite the substantial mortality reduction achieved with thrombolytic therapy, mortality remains unacceptably high. In addition, approximately 20% of patients require antifailure therapy following hospital discharge.

Thrombolytic therapy works by lysing occlusive coronary thrombi. If sustained patency is achieved, left ventricular function is improved and long-term survival is improved. Patency of the infarct-related artery is likely to be beneficial for preventing left ventricular remodeling and dilation, which has been shown to be the most important long-term prognostic factor after recovery from acute myocardial infarction. Long-term patency is also likely to decrease arrhythmogenesis and to provide collaterals if coronary artery occlusion occurs in a different artery in the future. Surprisingly, treatment with alteplase, which achieves earlier reperfusion than streptokinase or anistreplase, has not resulted in greater preservation of left ventricular function or improved survival. This is likely because early patency achieved with alteplase has not been sustained and the infarct-related artery has become reoccluded. Intermittent opening and closing of the artery may be more common after alteplase administration than following therapy with other thrombolytic agents, particularly if adequate antiplatelet and antithrombotic regimens are not given. Therefore, the early patency advantage may be lost. In addition, as early as 3 hours after administration, patency rates for streptokinase and anistreplase "catch up" and are equivalent. Whether earlier patency with alteplase can translate into clinical benefit remains to be answered.

Although alteplase appears to achieve high early patency, it is far from ideal. In the First Thrombolysis in Myocardial Infarction (TIMI-I) trial, even following 7 injections of contrast solution (which may open occluded arteries in 5–10% of patients), normal (TIMI grade 3) coronary artery flow at 90 minutes was achieved in only 34% of patients. Therefore, more than two thirds of patients do not achieve optimal early reperfusion—as judged by a 90-minute angiographic "snapshot" in time—even with alteplase. During the 24 hours that follow initial reperfusion, some arteries will open and close and some will become reoccluded. Clearly, there is far to go with regard to improving the efficacy of thrombolytic agents and decreasing reocclusion in the first 24 hours following acute myocardial infarction.

Beyond 24 hours, it appears that aspirin (160 mg/day) is sufficient to prevent reocclusion of most arteries. In the initial 24 hours, however, aspirin may not be sufficient, because it does not inhibit

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the powerful stimulus of thrombin to aggregate platelets. Heparin inhibits this thrombin-induced platelet aggregation and is likely to be very beneficial for achieving sustained patency. (There is no evidence that heparin has a differential beneficial effect with the various thrombolytic agents.) Heparin is likely to improve sustained patency with streptokinase and alteplase and also to reduce mortality. However, there will be increased bleeding with the administration of an earlier and more intensive heparin regimen, and the benefit-to-risk ratio needs to be tested in large clinical trials.

At present, all patients presenting within 6 hours with ST-segment elevation on the electrocardiogram and without contraindication to thrombolytic therapy should be treated. Treatment with a thrombolytic agent should be considered in most patients who present within 12 hours after symptom onset (and in some who present beyond 12 hours) and who have continuing pain. Patients with bundle branch block pattern should also be treated, as in all likelihood they have a proximal left anterior descending artery occlusion, and mortality is even higher than that for patients with large anterior infarctions. For patients with other electrocardiographic abnormalities, particularly ST-segment depression, treatment is not clearly indicated. These latter patients usually have a nonocclusive thrombus rather than an occlusive thrombus, and thrombolytic therapy is less likely to be beneficial. Also, thrombolytic therapy may have adverse effects, e.g., rarely causing elevation of plaque by subintimal hemorrhage and more commonly increasing platelet activation, which has a very important role in acute ischemic syndromes.

Further information is required for widening the current indications for thrombolytic therapy, particularly in terms of safety in patients with relative contraindications such as a history of remote stroke, menstruation, prolonged cardiopulmonary resuscitation, and concurrent warfarin therapy.

In this supplement, results from many recent trials are presented, with interpretations as to how these results may influence current clinical practice. Cardiologists are now faced with the challenge of how to improve patient care further from here. Improvement can be made in the efficacy and safety of thrombolytic agents, such as developing drugs that are selective for fresh clots. More specific antiplatelet and antithrombotic regimens must be developed, and the many interventions that may affect infarct expansion and ventricular remodeling need to be tested. The next few years will be very exciting and will, hopefully, bring good news for patients as the results of the various ongoing trials become available.

Importance of the Pharmacological Profile of Thrombolytic Agents in Clinical Practice

Joseph S. Alpert, MD

Three thrombolytic agents are frequently used in the United States for treating patients with acute myocardial infarction: streptokinase, alteplase (tissue plasminogen activator [t-PA]), and anistreplase (anisoylated plasminogen–streptokinase activator complex [APSAC]). A fourth agent, urokinase, is occasionally used but clinical experience is considerably more limited with this agent. Streptokinase, alteplase, and anistreplase differ in a number of pharmacologic properties, which include half-life, enzymatic efficiency, and induction of platelet aggregation; these differences may be clinically important. For example, anistreplase and alteplase have high affinity for fibrin and bind to intravascular thrombi after intravenous administration, which may result in higher clot specificity. Anistreplase has the longest half-life of the 3 agents and, therefore, can be administered conveniently and quickly. Alteplase has a shorter half-life and heparin is generally a necessary adjunctive agent. These differences can be clinically significant in various settings and application of such theoretical advantages is just beginning.

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Preservation of myocardium following coronary occlusion has been a goal of investigators and clinicians since the late 1960s. Initial efforts in this area focused on decreasing myocardial work demands.[1,2] More recently, thrombolytic agents have been demonstrated to restore blood flow to previously ischemic myocardium by dissolving occlusive coronary thrombi.[3–16] Intense clinical investigation has revealed that thrombolytic therapy salvages potentially necrotic myocardium, improves residual left ventricular function, and, most importantly, reduces in-hospital mortality in patients with Q-wave myocardial infarction.[12–16]

Streptokinase, alteplase, and anistreplase are the 3 commonly used thrombolytic agents in the United States for management of acute myocardial infarction. Urokinase is occasionally used but clinical experience is considerably more limited with this agent. Thrombolytic agents differ in pharmacologic properties, which may be important in determining efficacy, safety, and practical issues, such as timing and administration. For example, anistreplase and alteplase have high affinity for fibrin and, therefore, bind to intravascular thrombi following intravenous administration.[5,17] Unfortunately, this theoretical advantage has not yet been shown to translate into marked differences in terms of the end points of thrombolytic therapy (i.e., patency, reocclusion, left ventricular function, stroke, mortality). Each of the commonly employed thrombolytic agents differs with respect to ease of administration, half-life, enzymatic efficiency, and induction of platelet aggregation,[5,17] often leading clinicians to prefer one agent over another in particular clinical situations. For example, the ease of administration of anistreplase (a single injection given over 2–5 minutes) makes this agent particularly suitable for emergency department and prehospital (ambulance) administration.[18–21]

Reperfusion and patency rates for previously occluded coronary arteries have been similar for all thrombolytic agents in large clinical trials performed to date. Unfortunately, randomized, con-

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trolled, comparative trials have been few in number. Adverse events also appear to be similar in incidence for the 3 commonly employed agents. Theoretically, anistreplase may be associated with a lower and clinically significant reocclusion rate than the other thrombolytic agents because of its long half-life [5,20]

This brief review will examine and compare the pharmacology of urokinase, streptokinase, alteplase, and anistreplase in light of their clinical indications and utilization.

THROMBOGENESIS VERSUS THROMBOLYSIS

Thrombogenesis begins either with vessel-wall injury or a rupture or fissure of atherosclerotic plaque, thereby exposing highly thrombogenic elements in the underlying tissues to the circulating blood (Figure 1). Platelets begin to aggregate, as a result of the platelet-release reaction, and thromboplastin generated by platelet aggregation activates the clotting cascade. Prothrombin is then converted to thrombin, which, in turn, converts soluble fibrinogen to insoluble fibrin. A firm, adherent thrombus results with various blood elements trapped within the interstices of the fibrin network. It is important to remember that the various compounds and proenzymes of the fibrinolytic system are also trapped throughout this fibrin meshwork.

The endogenous thrombolytic system, activated whenever thrombi are generated, counters this thrombogenic reaction. The thrombogenic–thrombolytic system is an example of a biologic "reaction and counterreaction" system working to maintain homeostasis (Figure 2). Unfortunately, the thrombolytic system may become overwhelmed, thus requiring exogenous administration of thrombolytic agents. Exogenous thrombolysis is achieved by administering pharmacologic agents that also begin to dissolve the insoluble fibrin network generated by the thrombogenic reaction. Both the intrinsic system and extrinsically administered thrombolytic agents convert circulating and thrombus-bound plasminogen to plasmin.

Plasmin is an active enzyme that breaks fibrinogen cross-bridges and thereby dissolves thrombi. Circulating plasmin also destroys soluble fibrinogen within the circulation. The fibrin network within a thrombus is broken into small soluble pieces that can be detected within the blood as fibrin-split products. In another example of the "reaction/counterreaction" regulatory system, plasmin is deactivated by circulating α_2-antiplasmin, thereby decreasing the tendency toward large-scale, generalized thrombolysis throughout the body. When either intrinsic or extrinsic thrombolysis is set into action, the thrombus is attacked from within and from without. Activation of plasminogen trapped within the thrombus dissolves fibrin from within the clot while circulating plasmin breaks fibrin bridges on the thrombus surface.

CURRENTLY AVAILABLE THROMBOLYTIC AGENTS

Four thrombolytic agents are available for clinical use in the United States: streptokinase, urokinase, alteplase, and anistreplase. Clinically relevant pharmacologic properties of these agents are listed in Table I.

Streptokinase, urokinase, alteplase: Streptokinase is a bacterial enzyme that combines with circulating plasminogen to form a complex that

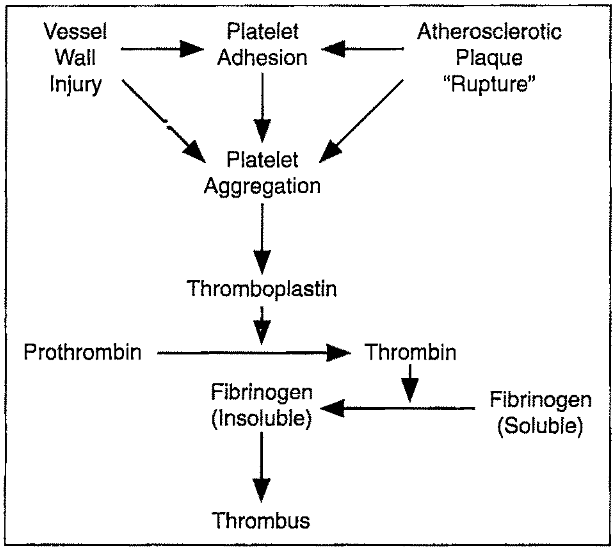

Figure 1. Mechanisms of thrombogenesis.

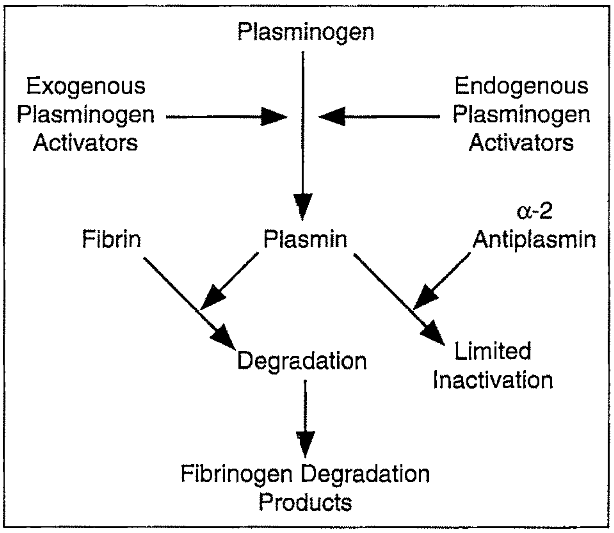
Plasminogen
Exogenous Plasminogen Activators
Endogenous Plasminogen Activators
Fibrin
Plasmin
α-2 Antiplasmin
Degradation
Limited Inactivation
Fibrinogen Degradation Products

Figure 2. Mechanisms of endogenous and exogenous thrombolysis.

TABLE I Pharmacological Profile of Available Thrombolytic Agents

Parameter	Streptokinase	Urokinase	Alteplase	Anistreplase
Enzymatic efficiency for clot lysis	High	Low	High	High
Fibrin affinity	Strong	Weak	Strong	Strong
Pharmacological half-life	Short	Short	Short	Long
Clot specificity	Low	Low	High	Moderate
Antigenicity	+	0	0	+
Transient hypotension	+	0	+	+
Hemorrhage as major adverse event	+	+	+	+

TABLE III Thrombolytic Agents: Pharmacological Considerations

Thrombolytic Agent	Administration Regimen	Plasma Half-Life of Circulating Fibrinolytic Activity (min)
Streptokinase	Infusion (1 h)	15–20
Urokinase	Bolus + infusion (1.5 h)	15–20
Alteplase	Bolus + complex infusion (90 min–6 h)	5
Anistreplase	Single injection (2–5 min)	90–120

actively splits circulating and thrombus-bound plasminogen to produce plasmin.[5,7,9,11,12] Plasmin, in turn, breaks insoluble fibrin cross-bridges, thereby leading to clot dissolution. Circulating soluble fibrinogen is also lysed; fibrin-split products are produced by both reactions. Urokinase, unlike streptokinase, is a mammalian enzyme that converts plasminogen to plasmin.[5,7,15,17] Unlike streptokinase, urokinase does not need to bind with plasminogen before an active reaction can occur. Once plasmin is formed, fibrin within a thrombus, as well as circulating fibrinogen, is lysed, yielding fibrin-split products. Alteplase is also a mammalian enzyme that actively converts plasminogen to plasmin in the presence of fibrin.[5,8,10,14] Thus, thrombolysis occurs only after alteplase binds to fibrin within a preformed intravascular thrombus. Circulating fibrinogen is lysed significantly less than is the case with streptokinase or urokinase.

Anistreplase: Anistreplase is a pharmacologically engineered molecule composed of lys-plasminogen and streptokinase bound together and *inactivated* by acylation of the enzymatically active center of the plasminogen molecule (Figure 3).[5,17–21] The anistreplase molecule cannot act on circulating plasminogen until spontaneous deacylation occurs in plasma,[21–23] thus generating the streptokinase–plasminogen (active) complex. The streptokinase–plasminogen complex then splits circulating and thrombus-associated plasminogen to plasmin as noted in the discussion of streptokinase. After conversion of plasminogen to plasmin, insoluble fibrin and circulating fibrinogen are lysed.

Because of less neutralization by plasma inhibitors and the slower degradation of anistreplase, anistreplase has considerably greater stability in plasma than does streptokinase.[17,20–22] High fibrin (clot) binding of anistreplase results in prolonged activity in the circulation. Moreover, the plasma half-life is longer with anistreplase than with any other thrombolytic agent (Tables I, II); thus, only a single dose is needed.[17,20–22]

Fibrin affinity: The fibrin-binding potential of anistreplase has been compared with that of alteplase and urokinase in 2 separate in vitro experiments.[20,24] In one study, the remaining serum concentrations of alteplase, anistreplase, and urokinase after plasma had been clotted with thrombin were

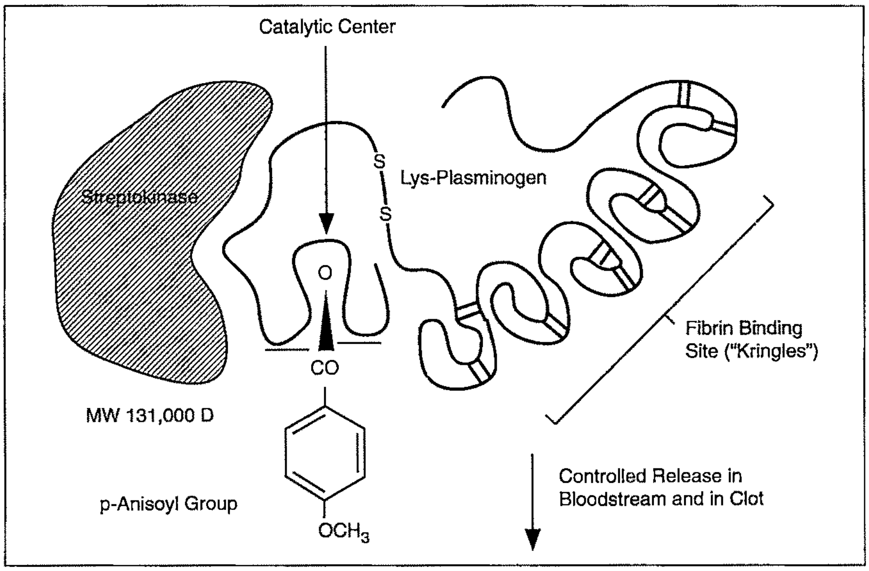

Figure 3. Molecular structure of anistreplase; MW = molecular weight.

TABLE III Comparison of Thrombolytic Agents for Reperfusion and Patency

End Point	Streptokinase (%)	Urokinase (%)	Alteplase (%)	Anistreplase (%)
Reperfusion	31–49	51–91	62–75	51–64
Patency	44–78	58–72	60–82	72–93
Reocclusion	~15	—	~15	7–8

compared. In a second study, relative uptakes of these thrombolytic agents into preformed human clots were assessed. In each study, both anistreplase and alteplase exhibited a high degree of fibrin binding (Figure 4). In contrast, urokinase demonstrated little or no fibrin affinity.[20,24]

Antigenicity: Streptokinase, because it is a bacterial protein, may occasionally cause allergic reaction (e.g., cutaneous rash, nausea, fever).[5] Allergic reactions following streptokinase administration are rarely anaphylactic (incidence 0.1%).[12] Anistreplase may also precipitate an allergic reaction in susceptible patients because it is a streptokinase-containing compound. Urokinase and alteplase are nonantigenic. When it is necessary to readminister a thrombolytic agent within 1 year of initial treatment, urokinase or alteplase are the preferred agents in patients who have previously received streptokinase or anistreplase.

Reperfusion following thrombolytic therapy: Reperfusion and patency rates are similar with anistreplase as with other thrombolytic agents (Table III).[25–31] Properties of anistreplase that contribute to its fibrinolytic potential include fibrin binding, long plasma half-life, and creation of a hypofibrinogenemic state in the bloodstream.[17] This latter property is the result of lysis of circulating fibrinogen. Low levels of circulating fibrinogen decrease the propensity for new thrombus formation even in the absence of heparin. Therefore, aggressive anticoagulation with heparin may be obviated, possibly decreasing the potential risk for hemorrhage.[17] Anistreplase generates in vivo fibrinolytic activity, which lasts for approximately 6 hours.

Hemorrhagic complications of thrombolytic agents: It is now clear that hemorrhage following administration of thrombolytic agents is not the result of low levels of circulating fibrinogen.[5,17] Agents that markedly decrease plasma fibrinogen levels (anistreplase, streptokinase, urokinase) have the same risk of bleeding associated with their use as do agents that decrease circulating fibrinogen to a more modest degree (alteplase).[5,17] Apparently, bleeding occurs in association with fibrinolysis when a hemostatic plug sealing an arterial injury (e.g., tear, rupture, fissure) is lysed by the thrombolytic agent. Preservation of circulating fibrinogen is no protection against such events. Indeed, bleeding complications have been similar with all 4 thrombolytic agents.

Rethrombosis following thrombolytic therapy: Platelet activation occurs whenever thrombolysis is initiated and likely results from exposure of fresh surfaces within a preformed thrombus as the fibrinolytic process proceeds.[5,17] Thus, the very act of thrombolysis sets off a platelet activation reaction that diminishes the beneficial effect of the thrombolytic agent. Platelet activation initiates a series of chemical reactions (i.e., the clotting cascade) that leads to thrombus generation. Hence, the recently reopened artery may close (rethrombose).

Agents that decrease circulating fibrinogen create a hypofibrinogenemic state, which works to

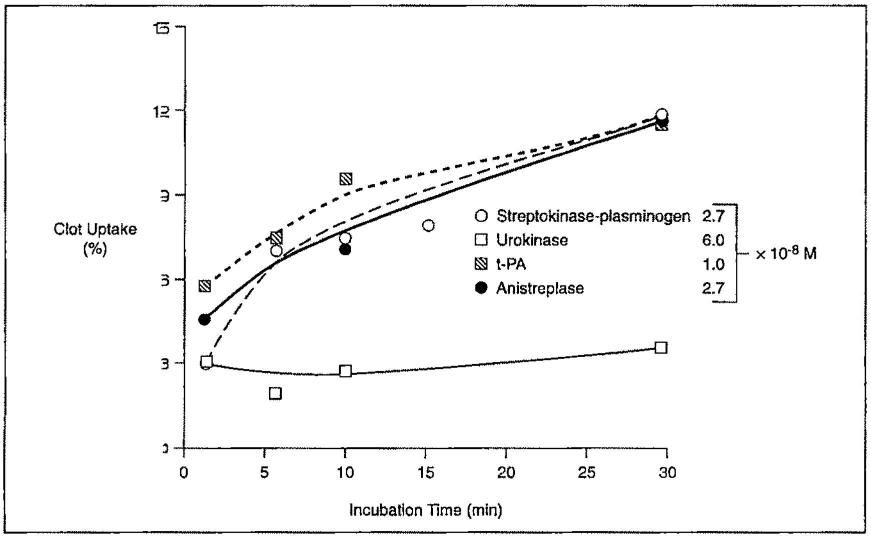

Figure 4. In vitro clot uptake of thrombolytic agents: streptokinase–plasminogen, urokinase, tissue plasminogen activator (t-PA, alteplase), and anistreplase.[20,24]

retard rethrombosis. Agents such as anistreplase, streptokinase, and urokinase fall into this category. Alteplase has a short half-life and decreases circulating fibrinogen less than these former agents and, therefore, is more often associated with rethrombosis. Meticulous heparinization is therefore more important when alteplase is employed to sustain reperfusion and prevent reocclusion. Anistreplase may be associated with the lowest incidence of reocclusion and heparin administration may not always be necessary.

CONCLUSION

Streptokinase, urokinase, alteplase, and anistreplase promote thrombolysis by ultimately activating plasminogen, either directly (urokinase) or indirectly (streptokinase, alteplase, anistreplase). However, differences are apparent in the pharmacologic profiles of these agents. Important differences exist among these agents and include half-life, fibrin specificity, early reperfusion, and reocclusion. Other factors to consider include ease of administration and cost. Many important questions remain unanswered with respect to advantages and disadvantages of the various thrombolytic agents. Currently ongoing, comparative clinical trials will shed considerably more light on these vital clinical issues during the next 10 years.

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Brief Overview of the End Points of Thrombolytic Therapy

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In addition to mortality, several measurable end points of thrombolytic therapy have been studied. These include coronary arterial patency, left ventricular function, reocclusion, reinfarction, and bleeding complications. Current wisdom dictates that recanalization of occluded arteries in the early phases of acute myocardial infarction should be attempted to preserve viable cardiac muscle, with the ultimate goal of decreasing mortality. Unfortunately, the number of patients eligible for thrombolytic therapy far exceeds the number receiving it, despite the clear benefits that have been demonstrated.

(Am J Cardiol 1991;67:8E–10E)

Results from multiple trials that have evaluated thrombolytic therapy in patients with evolving acute myocardial infarction have left the average cardiologist (including myself) dazed by sensory overload. This review will briefly summarize, from my own clinical perspective, 6 different end points of thrombolytic therapy: patency, reocclusion, left ventricular function, reinfarction, complications, and mortality, as published in the scientific literature or presented at national scientific meetings. These topics will be expanded further in subsequent articles in this supplement.

PATENCY

Coronary angiography performed 90 minutes following thrombolytic therapy provides an accurate assessment of the ability of thrombolytic agents to recanalize a thrombus-occluded artery rapidly. Patency of an infarct-related artery at 90 minutes after thrombolytic therapy in 10 major studies shows that alteplase (tissue plasminogen activator [t-PA]) has a higher patency than streptokinase.[1] If all studies of the available thrombolytic agents are considered, it is clear that alteplase and anistreplase (anisoylated plasminogen–streptokinase activator complex [APSAC]) have higher 90-minute patency rates than streptokinase. However, patency at 90 minutes may not be the best predictor of thrombolytic efficacy or mortality. When late patency is considered, differences between the thrombolytic agents become much less marked.

Patency and mortality: Many trials have shown that patients with open arteries have a lower mortality than patients with closed arteries. For example, in the Western Washington, Thrombolysis and Angioplasty in Acute Myocardial Infarction (TAMI), and Duke trials, lower mortality was observed in patients having open arteries at 1 year (2.5%, 7.1%, and 7.0%, respectively) compared with patients with closed arteries (15%, 10.4%, and 17%, respectively).

However, a question that must be addressed relates to the timing of the recanalization process.

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Does early opening of a coronary artery preserve myocardium and decrease mortality more than later opening? Intuition would suggest it does, but intuition has been wrong in the past. This aspect of patency and its relationship to mortality require further study.

LEFT VENTRICULAR FUNCTION

In every study performed, patients treated with streptokinase, alteplase, or anistreplase have a higher left ventricular ejection fraction than patients treated with placebo. Significant differences do not exist in terms of ejection fraction when streptokinase, alteplase, and urokinase are compared. Adjunctive agents such as captopril, β blockers, or calcium antagonists, when added to thrombolytic therapy, fail to increase the ejection fraction compared with thrombolytic therapy plus placebo. Unfortunately, patients with similar ejection fractions (ejection fraction equivalency), obtained with different thrombolytic agents, may not have the same mortality (efficacy equivalency). In other words, ejection fraction does not correlate well with survival.

Ejection fraction and mortality: Inverse relationships of ejection fraction and mortality were identified in 9 controlled thrombolytic trials.[2] Only one study showed that the increase in ejection fraction was associated with a decrease in mortality.[3] Failure to show that left ventricular ejection fraction correlates well with survival in these studies may be related to the following: 14% of patients die, 5–20% of patients had no ejection fraction measured, and the ejection fractions were technically inadequate in 10–20% of patients. In some instances, compensatory hyperkinesis may have increased the ejection fraction. Finally, the ejection fractions obtained from 7 days to several months after a myocardial infarction may not be appropriate because of several factors, such as the heterogeneity of ventricular loading conditions, the early effect of myocardial stunning, and drug effects.

REOCCLUSION

In the vast majority of patients, the occurrence of reocclusion or ischemia is unpredictable, occurring in approximately 15–20% of patients.[4] Reported rates of reocclusion for streptokinase and alteplase are approximately 15%; anistreplase is associated with lower reocclusion rates of 7–8%.[5–11]

When reocclusion does occur, there is a significant decrease in ejection fraction as well as an increase in mortality. Therapy with heparin, aspirin, and percutaneous transluminal coronary angioplasty (PTCA) have been ineffective in preventing reocclusion, as pointed out in the TAMI trials.[12] Also based on TAMI trials, reocclusion occurs most frequently during the first 24 hours. In addition, there is no difference in the ischemic zone regional wall motion in patients with a patent infarct-related artery. Recurrent ischemia can also occur without warning. In the TAMI trials, 29 variables were investigated, including quantitative coronary artery diameter stenosis, morphologic changes, demographics, and treatment. None of these predicted the reoccurrence of ischemia in patients with an open vessel who never underwent PTCA.

REINFARCTION

Using data from the Second International Study of Infarct Survival (ISIS-2) as a representative example, the reinfarction rate in this trial with streptokinase alone was 2.8%. When aspirin was added to this regimen, the reinfarction rate was slightly reduced to 1.8%.[13] This is approximately true in the other trials that have assessed the incidence of reinfarction as an end point of thrombolytic therapy.

MORTALITY

In all major trials of thrombolytic therapy, each of the available thrombolytic agents has been shown to decrease absolute mortality. Of particular concern is the use of thrombolytic agents in elderly patients. However, mortality declined in every trial that compared thrombolytic therapy with placebo and included elderly patients in the patient population. In fact, in patients receiving streptokinase and aspirin (ISIS-2), the number of lives saved per 100 patients treated in those <60 years of age was 2.5%. In contrast, for patients between the ages of 60 and 69, 7 lives per 100 patients treated were saved; in patients >70 years of age, 8 lives per 100 patients treated were saved. Similar results were observed in the Anglo-Scandinavian Study of Early Thrombolysis (ASSET) trial.[14] In the recently completed ISIS-3 trial, a significant reduction in mortality was observed in elderly patients treated with streptokinase, anistreplase, and duteplase (t-PA; Burroughs Wellcome).[15]

STROKE

All thrombolytic agents have been associated with stroke. In patients weighing >60 kg, the stroke incidence is approximately 1.1% with either streptokinase or alteplase. However, in patients weighing <60 kg, the stroke incidence is higher with alteplase (3.8%) than with streptokinase (1.2%) (unpublished data from the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico [GISSI-2]). In patients <70 years of age, the stroke incidence is approximately the same in patients receiving streptokinase and alteplase, but stroke incidence increases in the patients >70 years of age, particularly in the alteplase group, going from 1.5 to 2.7%.

BLEEDING COMPLICATIONS

In the Second Thrombolysis in Myocardial Infarction (TIMI-II) study, bleeding complications were increased with an increased dose of alteplase.[16] However, transfusions associated with bleeding were required in 7.7% of patients receiving 150 mg of alteplase versus 4.4% in patients receiving 100 mg of alteplase. Bleeding complications do not seem to be reduced with fibrin-selective agents. When considering altering drug levels by front loading, and increasing the dose of thrombolytic agents in order to open arteries more rapidly, remember that bleeding complications requiring transfusions were much higher in the patients who received higher doses of the drug. Intracranial hemorrhage, a catastrophic complication, occurs in about 0.5% of patients,[17] but there are no absolute predictive factors. Perhaps the weight of the patient must be considered and weight adjustment of the total dose given is important.

CONCLUSION

Current knowledge suggests that recanalization of occluded arteries in the early phase of acute myocardial infarction should be attempted to preserve viable cardiac muscle with the ultimate goal of decreasing mortality. In terms of patency, alteplase and anistreplase have higher patency rates than streptokinase at 90 minutes after thrombolytic therapy. Open coronary arteries 1 year after reperfusion are associated with a lower mortality than that found in patients with closed coronary arteries. Patients receiving thrombolytic therapy have a higher ejection fraction than those treated with placebo, but correlation with survival is not obvious. Reocclusion when it occurs is associated with a decrease in ejection fraction as well as with an increase in mortality. Reinfarction has a low recurrence rate when any of the thrombolytic agents are used. All thrombolytic trials decrease mortality compared with placebo, even in the elderly patient. Stroke incidence is low with all agents but may be increased in patients weighing <60 kg and in patients >70 years of age. Bleeding complications are increased with increasing doses of the thrombolytic agents. Intracranial hemorrhage has a low incidence with all agents but may be further reduced if weight and total dose are considered. Unfortunately, the number of patients eligible for thrombolytic therapy far exceeds the number of patients receiving it, despite the fact that numerous trials have indicated that those who receive thrombolytic agents clearly benefit.

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Overview of Patency as an End Point of Thrombolytic Therapy

Jeffrey L. Anderson, MD

Underlying the use of thrombolytic therapy is the hypothesis that reestablishment and maintenance of coronary blood flow (coronary patency) are the primary mechanisms of therapeutic benefit in patients with acute myocardial infarction. Early achievement and maintenance of adequate coronary blood flow (patency) in the infarct-related artery are the primary goals of thrombolytic therapy. One third of patients may achieve spontaneous patency within a few days following acute myocardial infarction. When antithrombotic therapy (i.e., heparin) is administered, this rate increases to >50%, but patency is achieved only gradually and mortality reductions comparable to thrombolytic therapy are not achieved. After administration of a thrombolytic agent, early (90-minute) patency rates are greater with alteplase or anistreplase than with streptokinase. However, patency rates for alteplase decline by 10–30% if intravenous heparin is not given concurrently. When patency is assessed >24 hours following thrombolytic therapy, no significant difference exists among the agents. A single angiographic observation of the artery at 90 minutes, although useful, may be inadequate to distinguish among the beneficial clinical effects of different thrombolytic regimens. The overall reperfusion or patency profile is probably a better basis for assessing relative benefits. Intravenous thrombolytic regimens that are increasingly effective in rapidly achieving and maintaining coronary patency are now available and in further development.

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Patency of the coronary artery after acute myocardial infarction (AMI) has appeared to be a logical end point for thrombolytic therapy since contemporary thrombolytic trials were begun in the early 1980s. Early trials were based on the intuitive hypothesis that benefits of thrombolytic therapy were primarily due to early reestablishment and maintenance of coronary blood flow ("patent coronary artery" hypothesis). For example, survival after intracoronary streptokinase in the Western Washington Randomized Trial[1] was 92% compared with 85% after nonthrombolytic, control therapy. However, in patients receiving streptokinase, 2 distinct subgroups were apparent: those achieving a patent coronary artery (98% survival) and those left with a partially patent or occluded coronary artery (85% survival, no better than control). Thus, it appears that it was not streptokinase per se that was responsible for improved survival, but streptokinase-mediated reperfusion. In AMI patients, differences in survival between groups with patent arteries and groups with occluded coronary arteries have been confirmed in other clinical studies.[2–4] This brief review will summarize selected patency (and reperfusion) studies that evaluate the standard, recommended administration regimens of the available thrombolytic agents.

PATENCY DEFINITIONS AND ASSESSMENT METHODS

Patency and reperfusion (or recanalization) are 2 technically distinct end points. Patency (open artery) is clinically defined by a single angiogram performed some time after therapy. Reperfusion, in contrast, requires pretreatment angiographic documentation of occlusion and demonstration of advancement to patent coronary artery status during or after therapy. Because 10–20% of coronary arteries are spontaneously patent at the time that AMI patients present for therapy,[5] the total patency rate will be higher than the true reperfusion rate by the percentage accounted for by spontane-

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ous patency. From the perspective of patient outcome, patency, no matter how achieved, is likely to be more closely associated with clinical outcome than reperfusion.

Patency can be assessed in different ways, depending on time of angiography and Thrombolysis in Myocardial Infarction (TIMI) grade. Although arbitrary, angiography at 90 minutes has been the most commonly used time end point. The maximum, or early plateau, patency rate (i.e., the maximum patency rate achieved at 1 day) may differ from the 90-minute rate and may occur somewhat later (or earlier) after particular thrombolytic regimens. The state of the coronary artery at hospital discharge has also been proposed as being prognostically important and, therefore, predischarge assessment of patency is common. Finally, patency can be assessed by its overall profile over time.

By grade, the sum of TIMI grades 2 (partial/delayed) and 3 (rapid/complete) has been most commonly used to assess patency.[4] However, TIMI grade 3 alone (complete perfusion) may be advocated as a better predictive end point.[1] In this regard, in our recent comparative study of anistreplase (anisoylated plasminogen–streptokinase activator complex [APSAC]) and streptokinase, the creatine kinase release curve distinguished patients with grade 3 flow at 90 minutes from other patients, showing a significantly lower, earlier peaking curve (unpublished observations); patients with grade 2 perfusion showed results closer to those with TIMI grades 0 or 1.

REVIEW OF CLINICAL PATENCY STUDIES

Comparisons with nonthrombolytic (control) therapies: Initial patency studies compared thrombolytic therapy with control (nonthrombolytic) therapy. Treatment with thrombolytic agents, not surprisingly, resulted in much greater rates of reperfusion or patency during the 1–2 hours of observation after administration. For example, the reperfusion rate at 60–90 minutes in the Western Washington Randomized Trial[1] averaged 68% after intracoronary streptokinase compared with 12% after control therapy with nitroglycerin. Similarly, in the European Cooperative Study,[6] treatment with another thrombolytic agent, alteplase (tissue plasminogen activator [t-PA]), resulted in significantly higher patency rates at 75–90 minutes than with placebo (61% vs 21%). A similar reperfusion advantage of anistreplase over placebo (56% vs 8%) also has been shown.[7]

Comparison between agents: After the mid-1980s, studies began to evaluate comparisons between different, but active, thrombolytic regimens. In early studies of intravenous streptokinase, patency was assessed using intracoronary streptokinase as the "gold standard." Reperfusion 60–90 minutes after intravenous streptokinase was variably less than after intracoronary streptokinase,[8,9] but patients seemed to do well clinically[10] and the ease of administration favored further development of the intravenous route of administration.

The TIMI-I study,[4] which compared alteplase with streptokinase, demonstrated a clear advantage of alteplase at the 90-minute end point regardless of whether reperfusion (62% vs 31%) or patency (70% vs 43%) was considered (both differences statistically significant).

At this point, the patency hypothesis becomes complicated; despite the early patency advantage for alteplase (in TIMI-I, the patency outcome ratio was 1.6:1, and in the European Cooperative Study,[11] 1.3:1), subsequent comparative studies show a ratio of 1:1 for left ventricular ejection fraction outcome[12] and 1:1 for mortality.[13] Therefore, either the patency hypothesis is flawed or the wrong patency end point was being measured in these trials.

When assessing patency, particular modifying factors must be considered. Findings from the TIMI-I trial[4] suggested that success after streptokinase administration, but not after alteplase administration, was more dependent on the age of the clot (i.e., the time to therapy from symptom onset). When treatment was given 4–7 hours after symptom onset, outcome (patency) after streptokinase was not as favorable as with alteplase (24% vs 55%). However, when streptokinase was given within 4 hours of symptom onset, the difference was not as marked (44% vs 61%). Also, an analysis of the reperfusion rate–time curves from the TIMI-I study showed that reperfusion rates had not plateaued at 90 minutes after streptokinase but were still rising.[4] In contrast, a plateau did begin to occur at 60–90 minutes after alteplase administration.

Moreover, the Pro-urokinase in Myocardial Infarction (PRIMI) Study[14] showed that, given additional time, streptokinase patency rates do "catch up" with other thrombolytic agents. In this study, streptokinase was compared with the fibrin-selective drug, pro-urokinase (single-chain urokinase-like plasminogen activator, saruplase, scu-PA). At 60 minutes, streptokinase was clearly behind in terms of patency (48% vs 72%, $p < 0.001$). However, at 90 minutes the gap narrowed (64% vs 71%), and by 24 hours the curves actually crossed over (88% vs 85%) and no significant difference between streptokinase and pro-urokinase in terms of patency was present.

Although alteplase is associated with a greater early patency rate than is streptokinase, the latter agent is associated with a lower subsequent reocclusion rate. In TIMI-I, for example, reocclusion rates were 14% and 24% for streptokinase and alteplase, respectively.[4] Studies have recently shown the important requirement for full-dose intravenous heparin after alteplase administration for maintaining optimal late (≥1 day) patency rates and preventing reocclusion. For example, in the Heparin Aspirin Reinfarction Trial (HART),[15] patency was significantly lower when aspirin (80 mg) was given instead of concurrent intravenous heparin (52% vs 82%, $p < 0.001$).

Approaches to improving the overall patency profile: Based on these observations, better thrombolytic regimens for both establishing and maintaining patency might include the use of combinations of fibrin-specific and nonspecific agents or improvements in the streptokinase or alteplase regimens themselves. For alteplase, front-loaded regimens are being tested, and concomitant full-dose, intravenous heparin is being advocated. For streptokinase, chemical modifications have been made by complexing streptokinase in vitro with lys-plasminogen, a more fibrin-avid form than the native, circulating glu-plasminogen, and temporarily blocking the active site on plasminogen with an acyl group, to form anistreplase.[16] In this form, anistreplase can be given as a bolus and achieves a long half-life of activity.

In an early European clinical trial comparing anistreplase with streptokinase in 86 patients with evolving AMI of <6 hours' duration, anistreplase showed a superior 90-minute patency rate to streptokinase (72% vs 56%, $p = 0.05$).[17] These results are similar to the patency superiority of alteplase over streptokinase, as seen in the European Cooperative Study (70% vs 55%).[11]

In a recently published multicenter study, the Second Trial of Eminase in Acute Myocardial Infarction (TEAM-2), we compared patency effects after treatment with anistreplase and streptokinase in 370 AMI patients within 4 hours of symptom onset.[18] Angiography was performed at 90–240 minutes. Adjunctive intravenous heparin was administered to both groups after 2–6 hours. As expected, the patency rate after anistreplase was high, 72%.[18] Surprisingly, total patency was similarly high (73%) after streptokinase (on the 2–2.5-hour angiogram), although grade 3 (complete) patency tended to be higher in anistreplase-treated patients (60% vs 53%).[18] Quantitative patency determinations also favored anistreplase, although modestly. The percentage of residual stenosis of the infarct-related artery (at 90–240 minutes) was 74% and 77% in anistreplase- and streptokinase-treated patients, respectively ($p < 0.02$).

A subsequent multicenter study (TEAM-3) compared anistreplase with alteplase.[19] In this comparison, 325 patients were enrolled within 4 hours of symptom onset and were randomized to standard doses of anistreplase or alteplase. Aspirin (162–325 mg) and full-dose intravenous heparin were given concurrently. Data concerning the primary end point, left ventricular ejection fraction, are not yet available. However, an important secondary end point was patency at 1 day, or the plateau patency achieved without interventions. These 1-day or plateau patency results of TEAM-3 have been presented in preliminary form and are gratifyingly high for both agents (90% for anistreplase, 85% for alteplase; difference not significant).[19] A comparison of individual patency grades (0, 1, 2, 3) also showed a similar profile for the 2 regimens. These data suggest that anistreplase produces high patency rates, both at 90 minutes[17] and at 1 day,[19] that are higher at 90 minutes than rates associated with streptokinase but very similar to results reported with alteplase.[11,19]

AN OVERVIEW OF PATENCY PROFILES FOR STANDARD THROMBOLYTIC REGIMENS

An overview of the patency profiles observed in available trials that evaluated standard regimens of anistreplase, streptokinase, and alteplase is presented in Tables I and II. This analysis is based on a complete search of the literature for all available

TABLE I Overview of Early Patency Trials* (90–240 minutes)

Thrombolytic Agent	No. of Studies	No. of Patients	Overall Patency (%)
Anistreplase	15	859	71.0
Alteplase	9	809	69.5
Streptokinase	10	745	65.5†

*See appendix for references.
†Nominally significantly less (chi-square analysis) than anistreplase or alteplase.

TABLE II Overview of Late (≥1 day) Patency Trials*

Thrombolytic Agent	No. of Studies	No. of Patients	Overall Patency (%)
Anistreplase	17	1,093	83.1
Alteplase	11	1,146	72.7†
Streptokinase	10	837	80.3‡

*See appendix for references.
†Nominally less than anistreplase and streptokinase.
‡Nominally less than anistreplase.

patency trial data. Careful and extensive use of commercial data bases—*Medline* and *Excerpta Medica*—ensured that all relevant studies were retrieved. Published abstracts of studies presented at major cardiology meetings were also included. This overview provided data on all trials published and presented up to December 1990.

Studies that used approved intravenous doses of the 3 available thrombolytic agents were selected. For anistreplase, the standard dose is 30 U, given over 2–5 minutes. For streptokinase, the standard dose is 1.5×10^6 U, generally given over 1 hour. For alteplase, the dosing regimen was equivalent to the administration of 100 mg over 3 hours (or less, i.e., ≥80 mg, as indicated, using a weight-adjusted schedule for lower-weight patients). Nonstandard or experimental dosing regimens, such as those using higher drug doses (e.g., 3.0×10^6 U streptokinase, or 150 mg alteplase) or accelerated regimens (e.g., front-loaded alteplase) were excluded. Studies that included the use of varied ancillary medications (e.g., aspirin or heparin) not shown to affect early patency were not excluded from the overview. Early patency was generally assessed close to 90 minutes, but within a range of 90–240 minutes. Late-patency studies were defined as assessments at a mean of ≥1 day.

Early patency was assessed in a total of 2,413 patients in 15 anistreplase studies, 9 alteplase studies, and 10 streptokinase studies. Late (plateau) patency was assessed in a total of 3,076 patients in 17 anistreplase studies, 11 alteplase studies, and 10 streptokinase studies. Results were averaged and compared for all studies on a per-patient basis.

For anistreplase and alteplase, average patency rates of approximately 71% and 70%, respectively, were achieved at 90–240 minutes (Table I). For streptokinase, the rate was lower (66%); the difference, however, is not as great as suggested by earlier studies[4] that used later thrombolytic treatment and/or earlier patency assessment.

Relative patency profiles at ≥1 day were somewhat different from results of early patency (Table II). Here, patency averaged 83% for anistreplase, 80% for streptokinase, and 73% for alteplase. Lower rates for alteplase may be due to the variable use of heparin, which appears to be an important adjunct for optimal late patency after alteplase, and may reflect the greater tendency for reocclusion after administration of this agent.[15]

Several overall patency profiles may be observed after AMI (Figure 1). Without antithrombotic therapy, about one third of patients may achieve spontaneous patency within a few days.[5] When heparin[20] (and possibly aspirin) is administered, this rate increases to >50%, but patency is achieved only gradually and reductions in mortality, as seen with thrombolytic therapy, are not achieved.[21] Ninety-minute patency is much greater after thrombolytic therapy, although it lags for streptokinase by a variable degree. Even greater and relatively comparable patency rates (≥80%) are present at 1 day and tend to plateau thereafter. However, patency rates for alteplase decline by 10–30% if intravenous heparin is not given concurrently.

CONCLUSION

The establishment and maintenance of coronary patency to improve survival in patients with

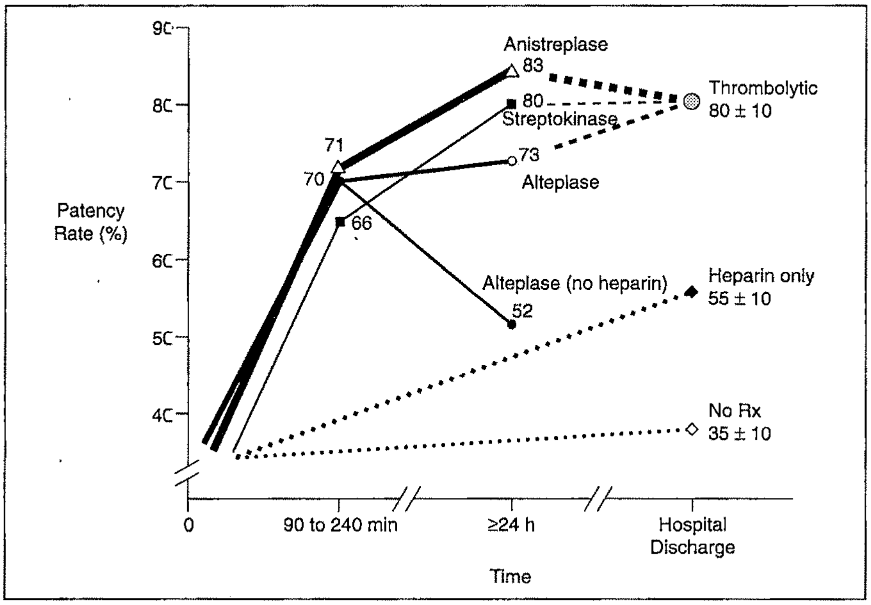

Figure 1. Overall patency profiles after acute myocardial infarction; based on an overview of patency studies (1986–1990) using standard (approved) regimens.

AMI are the chief goals of thrombolytic therapy. Data from numerous studies have shown that thrombolytic therapy markedly increases the percentage of patients achieving early reperfusion. Early patency rates differ among thrombolytic agents (anistreplase, alteplase > streptokinase), but differences are only modest after 90–240 minutes; later rates are higher and similar among agents (80±10%), provided that heparin is given with alteplase. Consideration of overall patency profiles of thrombolytic agents may better predict relative functional and mortality outcomes than 90-minute patency rates alone.

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APPENDIX:
References for Patency Overview (Tables I, II)

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Thrombolysis, Anticoagulation, and Reocclusion

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Based on apparent higher recanalization rates of the infarct-related artery, preferential use of thrombolytic agents with high clot specificity has been proposed for treating patients with acute myocardial infarction. In the Thrombolysis in Myocardial Infarction (TIMI-I) and European Cooperative Group studies, higher reperfusion rates were observed with alteplase compared with streptokinase, causing many to assume that the former would achieve a greater reduction in early hospital mortality. However, the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI-2) and its associated International Study Group failed to show any differences in 15-day mortality between these agents in more than 20,000 patients.

This apparent lack of correlation between reperfusion rates and early mortality may be explained in part when one considers that recanalization or patency rates measured at a given point in time, such as 90 minutes after onset of therapy, fail to define the subsequent vessel status. Early reocclusion is the major reason for this and is a major limitation to the clinical efficacy of thrombolytic drugs. Following recanalization, residual fibrin-bound thrombin adherent to the site of arterial injury from plaque rupture strongly promotes rethrombosis. Although antiplatelet and antithrombin agents such as aspirin and heparin help to decrease rethrombosis, these agents are far from ideal.

Thrombolytic agents that produce a significantly prolonged systemic thrombolytic state, such as streptokinase and anistreplase, are likely to result in less rethrombosis. Therefore, a systemic fibrinolytic state would appear to be an advantage rather than a disadvantage, particularly because the incidence of intracerebral hemorrhage does not appear to be greater with their use compared with agents producing less systemic fibrinolysis. Although relatively clot-specific agents producing only mild systemic fibrinolysis are associated with higher initial patency rates, they are also more likely to be associated with higher initial rethrombosis rates. Future therapy may be directed to the combined use of agents such as alteplase and streptokinase, alteplase and urokinase, or perhaps anistreplase alone to take advantage of early and higher recanalization rates produced by increased clot specificity combined with the advantage of a prolonged systemic lytic state. Results of the Third International Study of Infarct Survival (ISIS-3) and the currently planned Global Utilization of Streptokinase and t-PA for Occluded Arteries (GUSTO) trial may help to substantiate this approach.

(Am J Cardiol 1991;67:17E–22E)

Major clinical trials have demonstrated a substantial reduction in early mortality when patients experiencing acute myocardial infarction (AMI) with electrocardiographic ST-segment elevation are treated shortly after symptom onset with thrombolytic therapy.[1–4] Intuitively, one would expect thrombolytic agents that produce a higher early patency rate to produce the greatest improvement in survival. However, this is not necessarily true. The purpose of this review is to evaluate reocclusion as an end point of thrombolytic therapy and to put the available data concerning thrombolysis and anticoagulation into clinical perspective.

REOCCLUSION FOLLOWING THROMBOLYSIS

In a recent overview by Verstraete,[5] agents with fibrin (or clot) specificity, such as saruplase (prourokinase) and alteplase (tissue plasminogen activator) were associated with recanalization rates that were significantly higher than those seen with streptokinase, which tends to produce a systemic fibrinolytic state (statistical significance not reported) (Table I). Anistreplase (anisoylated plasminogen streptokinase activator complex), which produces a prolonged lytic state, has a patency rate

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TABLE I Recanalization and Patency Rates Following Thrombolysis*

	Before and After Treatment†		After Treatment	
Agent	Recanalization (%)	No. of Patients	Patency (%)	No. of Patients
Streptokinase	43	296	56	553
Urokinase	53	15	62	113
Alteplase	69	357	75	1,559
Anistreplase	56	196	77	288
Saruplase	67	56	71	198

*Modified with permission from *Circulation*.[5]

†Post-treatment angiography was performed 90 minutes following thrombolysis in almost all trials.

TABLE II Heparin Administration in Prethrombolytic Trials of Acute Myocardial Infarction

- 20 trials (5,700 patients analyzed)
- Heparin ≥20,000 U daily was administered in 90% of patients
- Subcutaneous administration in approximately 50% of patients
- Heparin-allocated patients had
  - 17% lower odds of death versus control
  - 22% lower odds of reinfarction
  - 50% lower odds of stroke

(at 90 minutes post-treatment) that is quite comparable with alteplase and much higher than streptokinase. The number of patients and mean times from pain onset to thrombolytic treatment varied in the studies that were included in this review; thus, recanalization and patency for the various thrombolytic agents cannot be directly compared.

Because of high patency rates reported in clinical trials, one might surmise that the use of agents such as alteplase would yield a mortality reduction greater than that achieved from the use of streptokinase. However, patency at a given point in time, such as the usual 90-minute measurement, is clearly only one factor that determines survival; *sustained* patency may prove to be more important. Interestingly, an increased likelihood for reocclusion may arise with the use of alteplase. Specifically, alteplase does not have antiplatelet properties and produces only a mild systemic fibrinolysis.[6] Furthermore, it has a very short half-life and, thus, reocclusion is quite likely to occur. The reocclusion rate with alteplase is approximately 15–20%.[7] Reocclusion following anistreplase administration is approximately 7–8%, half of that seen with alteplase.[8,9] These data may suggest that anistreplase is more likely than alteplase to produce sustained patency.

MORTALITY: THROMBOLYSIS AND HEPARINIZATION

Other than the Third International Study of Infarct Survival (ISIS-3; results soon to be published), only one major clinical trial (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico [GISSI-2]) has evaluated mortality in a head-to-head comparison of thrombolytic agents, namely, streptokinase and alteplase.[10,11] More than 20,000 patients were randomized in the GISSI-2 study and associated International Study Group to receive either streptokinase or alteplase. In addition, patients were further randomized to heparin (12,500 U given subcutaneously twice a day beginning 12 hours after thrombolytic therapy was initiated) or no-heparin treatment groups. Heparin therapy was evaluated to assess its effect on the incidence of early postinfarction ischemic events and overall outcome.[10] Hospital mortality in alteplase-treated patients was 8.9%; mortality in the streptokinase group was 8.5%. No difference in mortality was detected in patients who received heparin or no heparin, although there was an increase in bleeding in those patients who received heparin.

One must appreciate that at the time the GISSI-2 trial was initiated, concern had arisen as to whether bleeding complications (including hemorrhagic stroke) observed in prior thrombolytic trials were heparin-induced rather than attributable to the thrombolytic agent alone. Therefore, the use of intravenous heparin as adjunctive therapy was considered a potential problem. Furthermore, in the prethrombolytic era, significant data were available to show that subcutaneous heparin reduced mortality. In the overview by MacMahon and colleagues,[12] heparin-allocated patients in prethrombolytic heparin trials had a 17% lower odds of death than controls and about half of these trials evaluated subcutaneous rather than intravenous heparin (Table II). It would seem that the route of heparin administration has no effect on outcome.

In trials conducted in the post-thrombolytic era, there is also evidence of benefit from subcutaneous heparin administration. The Studio sulla Calciparina nell-Angina e nella Trombosi Ventricolare nell'Infarto (SCATI) trial[13] evaluated subcutaneous heparin (same dosage used eventually in the GISSI-2 trial) versus no heparin. Patients in the SCATI trial who arrived at the hospital <6 hours after symptom onset received streptokinase. These patients were further randomized to receive subsequent subcutaneous heparin or no heparin. The mortality rate for patients receiving heparin was 4.5%; mortality among patients who did not receive heparin was 8.8% ($p = 0.05$). These data suggest that subcutaneous heparin benefits patients who receive streptokinase. In contrast, no randomized clinical trial has evaluated the effect of intravenous heparin on mortality in patients receiving thrombolytic therapy. For all of these reasons, the heparin protocol in the GISSI-2 trial was an appropriate and rational decision.

RATIONALE FOR HEPARIN ADMINISTRATION

In patients with AMI, anticoagulation is important in the prevention of reocclusion and, ultimately, improvement in survival. Patients undergoing thrombolysis have residual fibrin-bound thrombin at the site of the arterial plaque rupture.[14] The residual thrombin is highly prothrombogenic; it tends to produce further fibrin formation as well as further fibrin cross-linkage that serves as a meshwork for clot stabilization. Thrombin also activates platelets with subsequent elaboration of serotonin and thromboxane A_2, which are not only vasoconstrictors but activate platelet fibrinogen receptors. Finally, the residual fibrin-bound thrombin stimulates the formation of prothrombinase. Prothrombinase is a complex formed from Factors Va and Xa along with calcium and the phospholipid surface of the platelet. Prothrombinase, in turn, converts prothrombin to thrombin at a rate approximately 5 orders of magnitude greater than would normally occur in its absence.[15] In short, residual thrombin bound to fibrin at the site of arterial injury following thrombolysis is the major culprit in producing rethrombosis. Therefore, it is of paramount importance to try to use a potent antithrombin drug, such as heparin, to prevent rethrombosis from occurring through the inactivation of thrombin surrounding the clot that is being lysed.

Clinically, one can predict which patients are at particular risk for reocclusion after successful reperfusion. Multivariate analysis has shown that independent variables that promote reocclusion in patients who had reperfusion and then developed subsequent reocclusion included the use of alteplase, reduced coronary blood flow, slow heart rate, and the right coronary artery being the infarct-related artery.[16] Reocclusion is of particular concern because it is associated with an increased hospital mortality. In the analysis of a large number of patients treated with thrombolytic agents, a patent infarct-related artery was associated with a mortality of 4%.[17] When the artery reoccluded, mortality was 12.8%. It is of interest, in light of the heparin controversy surrounding the GISSI-2 trial, that the use of alteplase proved to be an independent risk factor for reocclusion.

HEPARIN AND PATENCY

To date, no trials have directly compared subcutaneous with intravenous heparin in terms of patency or mortality. There are, however, trials that have evaluated intravenous heparin as adjunctive therapy in maintaining patency, and results have been inconsistent. Results from several trials have suggested little beneficial influence on maintaining patency,[18–20] whereas others suggest an important influence.

Among those trials suggesting that maintaining patency is of little benefit was the Third Thrombolysis and Angioplasty in Myocardial Infarction (TAMI-3) study, which compared patency 90 minutes after reperfusion with alteplase in patients receiving or not receiving intravenous heparin.[18] No differences in patency rates were observed. In the Australian Heart Foundation Study, all patients received heparin for 24 hours at full dosage.[19] Patients were then randomized to stopping heparin and starting aspirin and dipyridamole (each 300 mg/day) or continuing heparin therapy. At 7 days, there was no difference in ultimate patency: patency was 80% in both groups. In a trial at the Massachusetts General Hospital, 52 patients who experienced recanalization following alteplase were randomized to receive either an additional 4-hour infusion of alteplase (0.8 mg/kg) or heparin (1,000 U/hr).[20] Of the 27 patients who received heparin, 5 experienced reocclusion within 1 hour (angiographically documented). Finally, the patency rate in the First Thrombolysis in Myocardial Infarction (TIMI-I) trial was about twice as good with alteplase compared with streptokinase; however, reocclusion with alteplase was 24% and only 14% with streptokinase.[21] Angiographic repeat studies were performed between days 5 and 7, and patients were receiving full intravenous heparinization until repeat angiography was performed. In other words, the 24% reocclusion rate that occurred following recanalization with alteplase occurred despite the presence of intravenous heparin administration.

Although some data suggest that reocclusion occurs in the presence of heparin, a number of trials demonstrate benefit from intravenous heparin. In a recent trial by Bleich and colleagues,[22] 84 patients received alteplase (100 mg/3 hr) with or without intravenous heparin (5,000 U bolus followed by 1,000 U/hr). The heparin cohort had a patency rate of 71% compared with 43% in the controls at a mean of 55 hours. It should be noted that this was a comparison of intravenous heparin versus no antiplatelet or antithrombotic treatment; therefore, it is an inappropriate protocol design in terms of clinical relevance. In the Heparin-Aspirin Reperfusion Trial (HART),[23] heparin (5,000 U bolus, followed by 1,000 U/hour infusion) and aspirin (80 mg/day) was given to the control group (Figure 1). This dosage of aspirin was used because there are data in normal volunteers to suggest that low-dose aspirin is capable of inhibiting thromboxane A_2 synthesis.[24] However, the aspirin was swallowed and not chewed. Furthermore, this dosage of aspirin has never been shown to be appropriate in the acute infarct setting, where absorption of aspirin in the presence of a reduced cardiac output, and presumably splanchnic blood flow, may not be optimal. Finally, one would expect tremendous platelet stimulation and aggregation from fibrin-bound thrombin after plaque rupture and treatment with thrombolysis. Thus, the amount of aspirin that may be necessary to inhibit thromboxane A_2 formation is likely to be significantly higher than what is necessary in normal volunteers.

A significant number of patients (652) were randomized to receive either heparin or placebo in the trial of the European Cooperative Group.[25] In this trial the maintenance dosage of aspirin was low, but the majority of patients received an initial intravenous dose of 250 mg of aspirin. The patency rate among those treated with heparin was 83%; the patency rate among those who just received aspirin was 75%. It is interesting that the difference in this trial between heparin and aspirin was relatively small, with aspirin levels that were adequate during the first 24–48 hours. Assuming also that patients in GISSI-2 who received alteplase and subcutaneous heparin reoccluded at a rate as if they had received no heparin, one can speculate on what mortality would have been had intravenous heparin been used with the European Cooperative Group reocclusion results. If one assumes that there is a 20% mortality rate among patients with occluded arteries (rather than open arteries), mortality in the alteplase cohort randomized to subcutaneous heparin would have been approximately 7.5% in GISSI-2. This is not significantly different from the 7.9% mortality seen in the cohort receiving streptokinase and subcutaneous heparin in the trial, even without correcting for any benefit that might have occurred from using intravenous heparin.

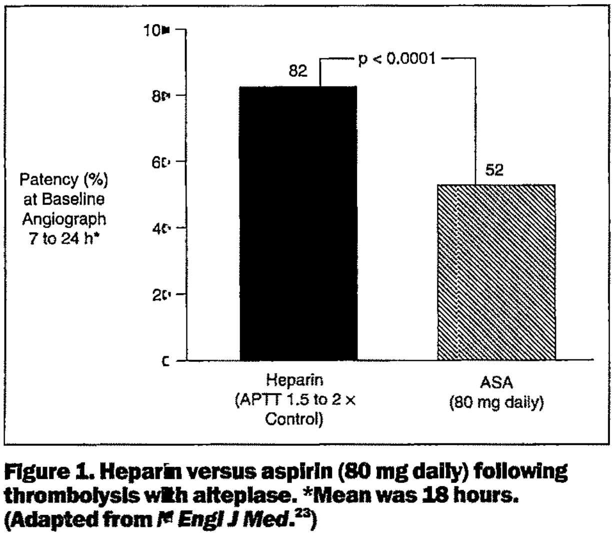

Figure 1. Heparin versus aspirin (80 mg daily) following thrombolysis with alteplase. *Mean was 18 hours. (Adapted from *N Engl J Med*.[23])

It is clear that heparin is an important drug and ideally should be used intravenously as guided by the activated partial thromboplastin time. However, it may not prevent reocclusion, even with full doses; furthermore, it may increase the occurrence of major bleeding. Obviously, better antithrombin drugs need to be developed. Weitz and colleagues[26] recently looked at the difference between fluid-phase heparin and other independent inhibitors of antithrombin III on clot-bound thrombin activity. With heparin, approximately a 20-fold higher concentration was necessary to block approximately 70% of clot-bound thrombin activity than was needed for equivalent inhibition of thrombin in plasma (Figure 2). This is not true, however, for other antithrombin drugs that tend to work with somewhat different mechanisms (e.g., hirugen or D-phenylalanyl-prolyl-arginine-chloromethyl-ketone [PPACK]).[26] Thus, compared to some of the newer experimental antithrombin drugs, heparin is relatively ineffective in preventing the thrombogenic effects of clot-bound thrombin.

Finally, a systemic fibrinolytic state is an important adjunct in the prevention of reocclusion. Intuitively, one may think that a systemic fibrinolytic state is to be avoided. In reality, systemic fibrinolysis may prove to be desirable. When we look at alteplase, which produces only a mild systemic lytic state, and compare the coagulation status of patients who developed reocclusion to those who did not, those with reocclusion had less of a change in plasma fibrinogen. These patients also displayed an increase in fibrin degradation products, which, in themselves, are anticoagulants. In other words, when you give alteplase and get more of a systemic fibrinolytic state (although it is relatively small compared with that produced by streptokinase), you are less likely to get reocclusion than if you produce less of a systemic fibrinogenemia.[27] Similarly, in recent studies of anistreplase, patency was maintained in patients who demonstrated a true lytic state.[28] However, in patients who failed to achieve a lytic state, adequate pa-

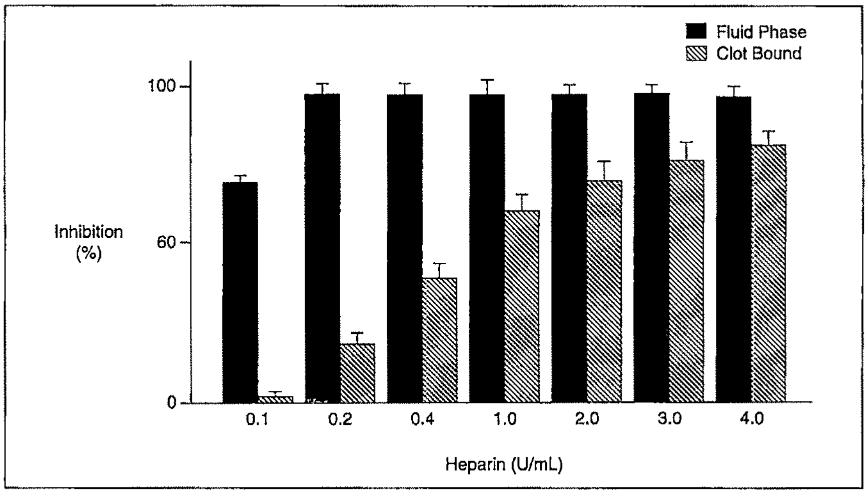

Figure 2. Effects of heparin on fluid-phase versus clot-bound thrombin activity. (Reprinted with permission from *J Clin Invest*.[28])

tency was not seen. These observations suggest that an ideal drug or a combination of drugs should have both a clot-specific activity that produces an early high patency rate and the capability of producing a subsequent sustained lytic state. Anistreplase is relatively fibrin-specific and induces a prolonged systemic state. We also know that the combination of alteplase and urokinase produces a small reocclusion rate, significantly better than we see with either drug alone.[29] A pilot study by Grines and colleagues[30] reported that patients receiving half-dose alteplase and full-dose streptokinase experienced a very low reocclusion rate. In an ongoing mortality study (GUSTO), 40,000 patients will be randomized to receive either streptokinase, alteplase, or the combination of streptokinase and alteplase. It will be interesting to see if this latter group does better.

CONCLUSIONS

Obviously, much work with antithrombin and antiplatelet agents to prevent reocclusion will be done in the future. Specific glycoprotein IIB/IIIA receptor blockade (either with monoclonal antibodies or with peptide sequences), the combination of thromboxane and serotonin receptor blockade, antibodies to von Willebrand factor, and prostaglandins, which inhibit platelet activity, are candidates for serious investigation. There is a recombinant DNA approach, the use of tissue plasminogen activator–antifibrin antibody combination (urokinase and platelet antibody proteins), antithrombin drugs (hirudin, hirugen, argatroban, PPACK), and activated protein C. The tick anticoagulant peptide is an interesting specific Factor Xa inhibitor and interrupts the coagulation process. These are all the subject of active investigations looking at the problem of reocclusion with the hope that we will reach a point where we not only have prolonged patency but can prevent reocclusion and thereby decrease mortality further with the use of thrombolytic therapy.

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Use of Left Ventricular Function as an End Point of Thrombolytic Therapy

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In recent acute myocardial infarction, early reperfusion of the infarct-related artery by intracoronary or intravenous thrombolytic therapy induces a significant limitation of infarct size, provided reperfusion occurs within a time frame that myocardial salvage can still be expected. Limitation of infarct size reduces scar tissue formation, aneurysm formation, infarct zone expansion, left ventricular volume enlargement, and eventually results in higher left ventricular ejection fraction. Infarct size limitation and left ventricular function preservation occur with all thrombolytic agents currently in clinical use: streptokinase, alteplase and, more recently, anistreplase. When anistreplase is compared with conventional heparin therapy, a 31% reduction in infarct size is found (estimated from single photon emission computed tomography, or SPECT). This translates into a significant preservation of left ventricular ejection fraction as observed in anistreplase-treated patients compared with heparin-treated patients (0.53±0.13 vs 0.47±0.12, $p < 0.002$). In comparative trials of 2 thrombolytic agents, anistreplase was demonstrated to be as efficient as alteplase on left ventricular ejection fraction preservation and infarct size limitation.

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The main goal of thrombolytic therapy in acute myocardial infarction (AMI) has been and continues to be the reduction in immediate and long-term mortality. Therefore, the primary end point that should be considered when assessing the efficacy of a given thrombolytic agent is the extent to which it influences mortality. However, estimating differences in mortality between 2 therapeutic options involves large trials. Several hundred patients and, in some instances, several thousand patients have been involved in various clinical trials comparing the thrombolytic agents currently in clinical use.[1-3] For many reasons (e.g., economic), one can assume that in the future, undertaking mega-trials for the development of any new thrombolytic agent or any new combination of thrombolytic agents will become increasingly difficult.

Early reperfusion of an infarct-related artery induces myocardial salvage, which leads to reduced mortality.[4] Therefore, assessment of reperfusion (and/or patency), reocclusion, left ventricular function preservation, and/or infarct size limitation as intermediate end points of the efficacy of thrombolytic agents is very tempting. The size of trials required for the study of such clinical end points is far smaller than that required for mortality studies.

These intermediate end points have been extensively used in the past and will probably continue to be used in the future. Among these intermediate clinical end points, myocardial salvage, left ventricular function preservation, and/or infarct size limitation are particularly important. In the past, left ventricular function, among other factors, has been shown to be a strong predictor of late outcome after myocardial infarction. In addition, left ventricular function preservation and infarct size limitation (due to early reperfusion of the infarct-related artery) were powerful determinants of mortality reduction. The purpose of this review is to analyze the efficacy of thrombolytic agents in terms of left ventricular function and myocardial salvage.

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LEFT VENTRICULAR FUNCTION AS A PREDICTOR OF OUTCOME IN MYOCARDIAL INFARCTION

In the past 2 decades, several reports have been published on left ventricular function as a predictor of long-term outcome following AMI. As early as 1973, Bruschke and colleagues[5] showed that the annual mortality rate from AMI was related to the contractile state of the left ventricle and the number of vessels involved. More recently, left ventricular ejection fraction has been shown to be a strong predictor of late outcome. De Feyter and associates[6] showed that the mortality rate in survivors of a first AMI was 22% over a 28-month follow-up period in patients with predischarge left ventricular ejection fraction <30%, whereas it was only 1% in patients with predischarge left ventricular ejection fraction >30%. Similarly, in the Multicenter Postinfarction Research Group[7] and in the study by Fioretti and colleagues,[8] left ventricular ejection fraction (<40%) was identified as a factor of poor prognosis. An inverse exponential relation was found between predischarge left ventricular ejection fraction at hospital discharge and 1-year mortality rate: the lower the ejection fraction, the higher mortality rate (Figure 1).[9]

Finally, in a study of 259 patients (followed up for an average of 34 months), Cox regression analysis identified left ventricular ejection fraction as the strongest predictor of late outcome.[10] In this series, other variables (among which end-diastolic volume also was shown to be a predictor of late outcome), higher left ventricular volume was associated with a higher mortality rate. The importance of left ventricular volume as a predictor of late outcome was demonstrated by White and colleagues,[11] who further confirmed the prominent prognostic contribution of left ventricular function after AMI. They followed up 605 patients for 78 months and showed that end-systolic volume was a more sensitive predictor of outcome than left ventricular ejection fraction. It is clear that left ventricular function is an important predictor of mortality in patients with AMI.

ASSESSMENT OF MYOCARDIAL SALVAGE AFTER THROMBOLYTIC THERAPY

In humans, measurements of myocardial salvage produced by a therapeutic intervention in AMI imply that either infarct size, recovery of left ventricular function, or both are estimated within hours or days after the administration of therapy. Conflicting results concerning myocardial salvage have been published. In most cases, methodologic considerations have limited the validity of the estimation of myocardial salvage. Indirect measurements of infarct size can be obtained from enzyme release[12] or from changes in the electrocardiogram.[13] Although these methods are widely used, they are probably less precise than direct estimation of thallium defect size in the area of the left ventricular wall that is jeopardized by the ischemic process. First introduced with thallium scans,[14] this technique has subsequently been tested and validated in laboratory animals with single photon emission computed tomography (SPECT), which allows a more accurate delineation of the defect size than thallium scans. Maublant and associates[15] developed a method with SPECT in which defect size is measured by summation of the number of pixels belonging to normal myocardium or to the defect on all of the scan sections passing through the myocardium. Infarct size is then expressed as a percentage of the entire myocardial volume. This method has allowed accurate determination of infarct size in laboratory animals.[15] In the clinical

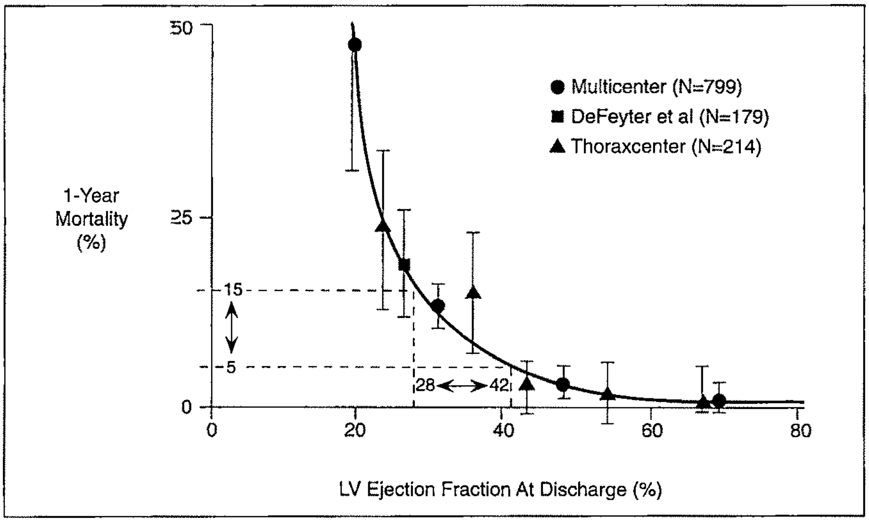


Figure 1. Inverse exponential relation linking left ventricular (LV) ejection fraction at hospital discharge to 1-year mortality rate. Reprinted with permission from *J Am Coll Cardiol*.[9].

field, this method has been used for estimating infarct size with an excellent reproducibility and low interobserver and intraobserver variabilities.[16] Similar methods derived from thallium-201 scintigraphy (using planar projections or tomographic sections) have also been used.[17,18] More recently, tracers other than thallium have been tested.[19]

Direct estimation of infarct size from SPECT contains known limitations linked to the pharmacokinetics of thallium-201 in the normal and ischemic myocardium. Experimental data have shown that myocardial defect size varies over time and that very early measurements may lead to incorrect estimations of infarct size.[14] It is known from experimental data that timing of thallium administration after restoration of coronary blood flow will greatly influence uptake, washout patterns, and, therefore, perceived defect size.[20] Soon after reperfusion, an excessive thallium uptake occurs in the infarct zone due to increased blood flow. Because initial uptake is related to blood flow (whereas redistribution is a marker of cell viability), redistribution images more appropriately reflect the actual infarct zone than the images taken soon after the infusion of thallium (if imaging is undertaken within hours following reperfusion).[20] Moreover, full recovery of metabolism and function within the infarct zone may be delayed as long as 10–12 days after reperfusion.[14]

In the clinical field, serial studies have shown that defect size in reperfused patients decreases from measurements made within the first hours to those made on the fourth day, and even those performed during the sixth week.[21] This phenomenon may indicate that in these patients, persistent defects are not related to an irreversibly damaged myocardium, but rather to severe ischemia, and recovery of thallium uptake in the ischemic area may still occur after several days. Therefore, it is recommended that the defect size be estimated long after reperfusion has occurred and preferably from redistribution images to avoid any possible bias in estimating infarct size. Optimal timing to perform studies may well be during the second week after symptom onset.[14]

Because a relation exists between infarct size and left ventricular function, measurements of left ventricular function provide valuable, although indirect, information concerning the mass of the infarcted myocardium.[22] However, for many reasons, it is mandatory to analyze regional as well as global left ventricular function to avoid any misinterpretation of data. Regional contraction patterns in a noninfarcted area greatly influence the accuracy with which the left ventricular ejection fraction indicates the severity of the depressed contractility in the infarcted zone. Regional function can be enhanced or, on the contrary, depressed in the noninfarcted area during the first days of the evolution of the AMI.[23,24] Global left ventricular ejection fraction is the result of complex interactions between the infarcted region wall motion and the noninfarcted region. Therefore, for a correct appreciation of the potential beneficial effects of myocardial reperfusion, measuring regional wall motion with angiography, radionuclide angiography, or even with 2-dimensional echocardiography (in addition to the global left ventricular ejection fraction) is mandatory. Moreover, these measurements are essential to have an accurate idea of the actual amount of myocardium destroyed by both the ischemic process and reperfusion lesions.

Timing of the evaluation of left ventricular function also is of major importance. For reasons previously mentioned, full recovery of contraction in the reperfused area occurs only 10–12 days after reperfusion.[25] A longer duration of ischemia is associated with a longer delay before full recovery.[25] Estimates of residual left ventricular function should therefore be delayed up to the end of the second week following symptom onset.[26] Delaying the measurement of residual left ventricular function may increase the risk of missing values due to death or patients lost to follow-up. Therefore, when dealing with left ventricular function as an end point, missing values must be given the worst score if they are not equally distributed between the 2 series under consideration.[27]

CURRENT RESULTS WITH VARIOUS THROMBOLYTIC AGENTS

Streptokinase: Various trials have failed to show significant differences in left ventricular function between patients receiving streptokinase and patients receiving placebo. In the Western Washington Intracoronary Streptokinase Trial,[28] differences in left ventricular ejection fraction and infarct size were not significant. However, patients in this study were randomized up to the 12th hour following symptom onset. This time for randomization was far beyond the time window during which myocardial salvage and left ventricular function preservation from reperfusion can be expected.[28]

Conversely, in trials in which the inclusion period was ≤ 6 hours following symptom onset, preservation of left ventricular function and reduction in left ventricular volume were significant. In the Netherlands Interuniversity Cardiology Institute Trial (intracoronary streptokinase versus placebo),[27] left ventricular ejection fraction was significantly higher and left ventricular volume was significantly lower in the therapeutic group than in the placebo group. Similarly, a significant preservation of left ventricular function after administration of intravenous streptokinase was found in the ISAM study[29] and in the study of White and colleagues.[30]

In the Western Washington Intravenous Streptokinase Trial, the difference in left ventricular ejection fraction was highly significant in patients with anterior wall infarction but not in those with inferior wall infarction. However, in the whole population, the difference in left ventricular ejection fraction was minimal.[18,31] Interestingly, only a fraction of the population was studied in this trial. In a small, comparably designed trial,[32] similar results in terms of improved left ventricular ejection fraction and lower left ventricular volume were observed in the subgroup of patients with anterior wall infarction compared with the patients in the placebo group.

Alteplase: Most of the trials in which alteplase (tissue plasminogen activator) was used for an analysis of left ventricular function have demonstrated that this thrombolytic agent is capable of inducing a limitation of infarct size or preservation of left ventricular function. In the National Heart Foundation of Australia Coronary Thrombolysis Group,[33] 144 patients were randomized (within 4 hours after symptom onset) to 100 mg alteplase or placebo. Left ventricular ejection fraction was significantly higher in patients receiving alteplase (57.7 vs 51.7, $p = 0.04$). The difference in anterior wall infarction was higher (52.7 vs 40.0, $p = 0.02$). In a comparably designed trial[34] of 145 patients (<2.5 hours after symptom onset), similar results were reported. Left ventricular ejection fraction, estimated from contrast and radionuclide ventriculography, was significantly higher in the therapeutic group (61 ± 13 vs 54 ± 14, $p = 0.06$) at 3 weeks. The improvement of left ventricular ejection fraction was higher in patients with anterior wall infarction.

Data from the European Cooperative Study Group,[35] in which more than 700 patients were randomized, showed a 20% reduction in infarct size and a significant preservation of left ventricular ejection fraction. The difference in left ventricular ejection fraction between alteplase- and placebo-treated patients, although statistically significant, was relatively low. However, the percentage of missing data concerning left ventricular ejection fraction in this study was high, approximately 20% of the study population.

Anistreplase: Myocardial salvage has been estimated in several studies using very different methods, which have sometimes produced conflicting results. In their first report, Been[36] and coworkers randomly allocated 32 AMI patients to placebo or to anistreplase (anisoylated plasminogen–streptokinase activator complex [APSAC]) within 3 hours following symptom onset. Left ventricular systolic function was measured from radionuclide angiography before hospital discharge. In patients with anterior wall infarction, left ventricular ejection fraction was higher in the anistreplase group than in the placebo group (37% vs 23%). The difference was not significant in patients with inferior wall infarction.

In an open study,[37] 73 patients were submitted to conventional therapy (controls) and 76 patients were submitted to thrombolysis with anistreplase within 4 hours following symptoms onset. Myocardial salvage was assessed by means of total creatine kinase (CK)-isoenzyme release and QRS score. In the anistreplase group, a 12% reduction in the QRS score was observed. The difference was more important in patients who received anistreplase within 2.5 hours following the symptom onset. In contrast, no reduction in total CK-isoenzyme release was found.

In the German Multicenter Trial of anistreplase and heparin, global and regional ejection fractions were estimated.[38] Patients (313) were randomly allocated (within 4 hours following symptom onset) to heparin or to anistreplase (30 U). No difference in global or regional ejection fraction measured at week 3 was found between the 2 treatment groups, although a significant reduction in mortality was observed at week 4. Similarly, no difference in the enzyme release appeared between the 2 groups.

In the APSAC in Myocardial Infarction study, 231 patients were randomized (within 5 hours following symptom onset) to heparin or to anistreplase (30 U) according to a double-blind, double-dummy procedure.[39] At early analysis, left ventricular ejection fraction was significantly higher in the anistreplase group than in the heparin group (53% vs 47%, $p < 0.002$); this was true for the anterior infarct subgroup (47% vs 40%, $p < 0.04$) and the inferior infarct subgroup (56% vs 51%, $p < 0.03$) (Figure 2). At late evaluation (3 weeks after symptom onset), however, part of the difference observed at early estimation was offset. The difference in left ventricular ejection fraction between the 2 treatment groups remained significant for the

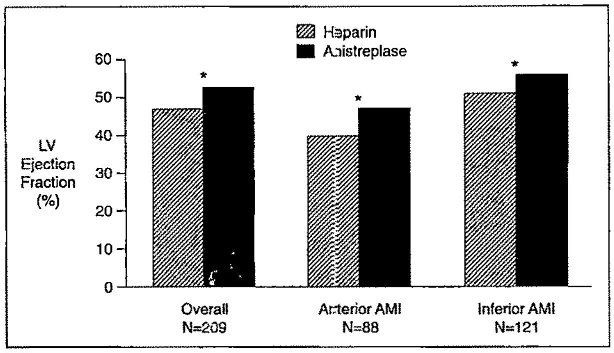


Figure 2. Results of the left ventricular ejection fraction determined on average on day 4 from contrast angiography. Left ventricular (LV) ejection fraction is significantly higher in the anistreplase group than in the heparin group (*p < 0.01). Overall=whole group; AMI=acute myocardial infarction.

study population as a whole and for the anterior infarct subgroup. However, the difference between anistreplase and heparin patients had vanished in the inferior infarct group. Significant differences were observed in regional wall motion between the 2 treatment groups, namely, in the anterior and septal areas in the anterior infarct subgroup and in the septal area in the inferior infarct subgroup. Infarct size was significantly lower in the anistreplase group than in the heparin group. This was true for the whole group and for the anterior infarct group but not for the inferior infarct group (Figure 3). A strong relation was found between left ventricular ejection fraction and infarct size, measured at 3 weeks, in both treatment groups (Figure 4).

COMPARISON AMONG THROMBOLYTIC AGENTS

Few studies have compared the efficacy of different thrombolytic agents with left ventricular function as an end point. In the First Thrombolysis in Myocardial Infarction (TIMI-I) study,[40] no significant difference in left ventricular ejection fraction was observed in patients randomized to alteplase or streptokinase. In a comparison of the respective efficacy of alteplase (100 mg over 3 hours) and intravenous streptokinase (1.5 × 10^6 U over 30 minutes), investigators failed to find any significant difference in terms of left ventricular ejection fraction and left ventricular volume between the groups.[41] Similarly, in the Plasminogen Activator Italian Multicenter Study (PAIMS),[42] differences in terms of left ventricular ejection fraction were not significant in patients receiving streptokinase

Figure 3. Results of infarct size. The difference between the 2 treatment groups is significant in the whole group as well as in the subgroup of anterior infarcts (*p < 0.01). Conversely, in the inferior infarcts the difference is not significant. SPECT=single photon emission computed tomography.

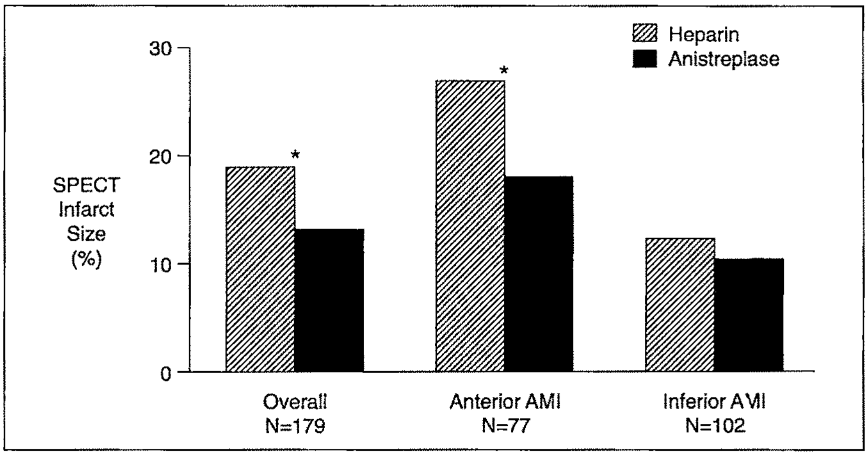
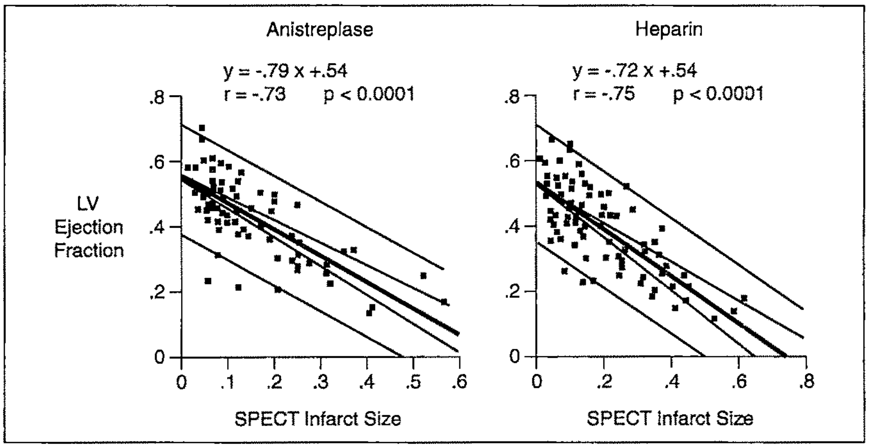


Figure 4. Close inverse linear relation linking infarct size and left ventricular (LV) ejection fraction at the third week. The slope of the relation is steeper in the anistreplase group than in the heparin group because left ventricular ejection fraction is higher and the infarct size is lower in the former than in the latter treatment group.



or alteplase. Interestingly, the percent change of left ventricular ejection fraction from admission to hospital discharge was higher in the alteplase group than in the streptokinase group.

In the first direct comparison of alteplase and anistreplase (100 mg over 3 hours and 30 U over 5 minutes, respectively), we failed to find any significant difference in terms of left ventricular ejection fraction and infarct size between the 2 therapeutic regimens among 183 randomized patients. Both drugs were shown to be equally efficient, in terms of infarct size and left ventricular function, and equally safe in terms of bleeding complications and side effects.[43]

CONCLUSIONS

Estimation of the beneficial effects of early reperfusion with thrombolytic agents on infarct size and left ventricular function is an important issue in patients with AMI. The size of the trials required to address such an issue is far smaller than what is necessary to demonstrate an improved survival. Left ventricular function studies must preferably be carried out several days after symptom onset because full recovery of myocardial function and metabolism is delayed by 10–12 days after the occurrence of reperfusion. For similar reasons, myocardial perfusion studies must be performed long after reperfusion has occurred to avoid any underestimation of the myocardial thallium defect and, thus, to avoid any misinterpretation of infarct size and myocardial salvage.

In the clinical field, streptokinase, alteplase, and anistreplase significantly reduce infarct size and preserve left ventricular function when compared with conventional therapy. Similarly, in trials in which 2 thrombolytic agents are compared, no significant differences in terms of myocardial salvage are observed. Anistreplase is as efficient as alteplase on left ventricular ejection fraction preservation and infarct size limitation.

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Comparative Safety of Thrombolytic Agents

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Three available thrombolytic agents, streptokinase, alteplase, and anistreplase, have been shown to have similar effects on preservation of left ventricular function and mortality reduction after acute myocardial infarction (AMI). The agents are, however, quite different with respect to their safety profiles. Clinical trials to date suggest that alteplase (tissue plasminogen activator) or anistreplase administration is associated with a high incidence of cerebral hemorrhage. In contrast, streptokinase is associated with a low rate of cerebral hemorrhage. Streptokinase and anistreplase are associated with a higher risk of allergic reaction when compared with alteplase. Hypotension is also more common with streptokinase and anistreplase, but occurs significantly with alteplase as well. Alteplase is associated with a lower reinfarction rate when compared with streptokinase and anistreplase. The Third International Study of Infarct Survival (ISIS-3), a direct comparison of 3 thrombolytic agents (streptokinase, anistreplase, and duteplase), may provide some insight regarding the safety of these agents. Because these agents have been shown to be equally effective, selection of an appropriate agent for an individual patient may depend more on assessment of the likelihood of an adverse event or other factors, such as cost or convenience of administration, rather than assessment of the probability of greater benefit with a particular agent.

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Streptokinase, alteplase (tissue plasminogen activator [t-PA]), and anistreplase (anisoylated plasminogen streptokinase activator complex [APSAC]) all lyse clots by producing plasmin and have been shown to have the same effects on reduction of mortality[1–6] and preservation of left ventricular function after acute myocardial infarction.[7,8] These agents differ, however, in terms of allergy, hypotension, bleeding, and stroke incidence. Large, randomized, comparative trials have also shown differences in reinfarction rates among these drugs.[5,6] There is considerable controversy as to whether the mortality benefit with each agent may be different with different dosing and heparin regimens.[9] A large, comparative trial is currently in progress to evaluate specific thrombolytic and heparin regimens. The purpose of this review is to compare and contrast the safety profiles of thrombolytic agents in terms of stroke, bleeding, allergy, hypotension, reinfarction, and mortality.

SAFETY OF THROMBOLYTIC THERAPY

Comparisons with control treatment: Overall, thrombolytic therapy has been shown to be surprisingly safe, given the standard contraindications for treatment. As thrombolytic therapy began to be widely used in the community, there was considerable concern about major bleeding, cerebral hemorrhage, reperfusion arrhythmias, and reinfarction. Consequently, it was thought that patients would need to be treated in tertiary centers with facilities for acute angioplasty.

Fortunately, clinical trials have shown that the benefits of thrombolytic therapy far outweigh the risks in most groups of patients. The incidence of major bleeding (requiring transfusion and in the absence of cardiac catheterization) after administration of a thrombolytic agent is $<1\%$.[4–6] Although the incidence is relatively low, cerebral hemorrhage continues to be a major concern. In the Second International Study of Infarct Survival (ISIS-2), however, treatment with streptokinase did not increase overall stroke rates, since the incidence of thrombotic and ischemic stroke was decreased (Table I).[2] Reperfusion arrhythmias have

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TABLE I Percentage of Adverse Events in ISIS-2[2]

Event	Streptokinase (n = 8,490)	Placebo (n = 8,491)	Difference
Cardiac arrest			
VF	4.4	5	−0.6
Other	4.4	5.1	−0.7
Stroke			
Hemorrhagic	0.08	0	+0.1
Other	0.63	0.79	−0.2
Any	0.71	0.79	−0.1
Bleeding	0.5	0.2	+0.3
Reinfarction	2.8	2.4	+0.4

VF = ventricular fibrillation.

not been troublesome and do not require special treatment. In ISIS-2, streptokinase therapy was associated with a reduction in cardiac arrest during hospital admission (Table I). Antithrombotic therapy with aspirin following administration of thrombolytic agents has resulted in reinfarction rates (at 1 month) of <5%. In contrast, randomized trials have shown that angioplasty does not reduce the incidence of reinfarction and should be reserved for symptomatic patients. Major allergy (anaphylaxis) following thrombolytic therapy has been rare.

Comparison among agents: The frequency of adverse events with thrombolytic agents is low. However, conclusions cannot be drawn from small, noncomparative trials. Comparisons need to be made in large numbers and in the same types of patients. The Second Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2)/International study[5] and ISIS-3[6] have been able to provide important comparative data. Although it is possible that some underreporting of adverse events may exist in large mortality trials, there should be no bias in terms of the thrombolytic agent involved.

Stroke: Whether fatal or disabling, stroke is the most devastating adverse effect of thrombolytic therapy. For this reason, patients at high risk, such as those with a history of previous or recent stroke or hypertension on admission, have usually been excluded from clinical trials.

Prior to the thrombolytic era, stroke occurred in 1.7–2% of patients, was more common in patients with anterior infarctions,[10] and cerebral hemorrhage was rare. In the thrombolytic era, the reported incidence of stroke has been lower, possibly due to exclusion of high-risk patients. Depending on the frequency of computed tomography scanning, intracerebral bleeding has become a much more common cause of stroke.

In the Thrombolysis in Myocardial Infarction (TIMI) trial,[11] the cerebral hemorrhage rate was unacceptably high following alteplase 150 mg, a higher-than-recommended dose. Comparison between thrombolytic agents in the present discussion is with the standard recommended doses. Although concomitant use of aspirin or heparin may have different effects on the frequency of adverse effects with the different thrombolytic agents, these differences are likely to be small.

Prior to the preliminary report of ISIS-3 comparing the 3 agents,[6] analysis of more than 50,000 patients showed that streptokinase had a low intracerebral hemorrhage rate (0.17%),[1,2,5,7,12–24] anistreplase had an intermediate rate (0.3%),[3,19,22,23,25–51] and alteplase a high rate (0.49%),[5,7,18,46,52–68] with the total stroke frequency 2–3 times higher for each agent (Table II). Because the populations and reporting rates may be different in trials that are not direct comparisons between the agents, these incidences should not be interpolated as showing statistical differences.

In the direct comparison of alteplase and strep-

TABLE II Incidence of Total Stroke and Intracranial Hemorrhage

Trial	Percentage			p Value
	Streptokinase	Alteplase	Anistreplase	
All[1–4] (excluding GISSI-2 and ISIS-3)				
Number of patients	17,069	10,036	3,372	
Total stroke (%)	0.34	1.25	0.86	
Intracranial hemorrhage (%)	0.08	0.49	0.30	
GISSI-2/International Study[5]				
Number of patients	10,396	10,372		
Total stroke (%)	0.94	1.33		<0.01
Intracranial hemorrhage (%)	0.29	0.42		0.16
ISIS-3[6]*				
Number of patients	12,848	12,841	12,885	
Total stroke (%)	1.14	1.51	1.45	0.02
Intracranial hemorrhage (%)	0.30	0.73	0.58	0.0001

*Duteplase was used in this study instead of alteplase.

tokinase by the GISSI-2 and International Study groups, the incidence of total stroke was higher in alteplase-treated patients (1.33% vs 0.94%, $p < 0.01$).[5] In this trial, there appeared to be a difference between the agents in terms of total stroke risk in patients >70 years of age. For patients <70 years of age, the stroke rates were 0.8% for streptokinase and 0.9% for alteplase, whereas for patients >70 years of age, stroke rates were 1.6% for streptokinase and 2.7% for alteplase ($p=0.02$).[5]

As shown in the large mortality trials comparing various thrombolytic agents to placebo or control, the benefits of thrombolytic therapy are greater in the elderly.[2-4] No excess of total stroke or cerebral hemorrhage with streptokinase therapy compared with placebo was observed in older patients in ISIS-2[2]. Elderly patients should not be denied thrombolytic therapy. A lower incidence of stroke may be observed if streptokinase is used instead of alteplase in this population.

In ISIS-3, the total stroke rate was lowest in streptokinase-treated patients (1.1%) (Table II). Duteplase (t-PA; Burroughs Wellcome) and anistreplase were associated with a similar incidence of stroke (1.5%). The incidence of ischemic stroke was similar for each of the 3 agents, with the excess for duteplase and anistreplase being due to early cerebral hemorrhage.[6]

Stroke and heparin therapy: In the GISSI-2/International Study, patients were randomized 12 hours after initiation of thrombolytic therapy to either no heparin or heparin (12,500 U subcutaneously twice daily for 1 week).[5] Heparin therapy was not associated with an increase in either hemorrhage or total stroke. In ISIS-3, patients who received heparin (12,500 U subcutaneously twice daily) were randomized 4 hours after beginning thrombolytic therapy with streptokinase, duteplase, or anistreplase.[6] Heparin did not increase the total stroke incidence (minus 1 stroke per 1,000 patients treated), but it did increase the incidence of cerebral hemorrhage by 2 per 1,000 patients treated.

Heparin therapy is likely to have its greatest benefit (and risk) when administered (intravenously) early, by decreasing the incidence of reocclusion of reperfused infarct-related arteries.[54,61] Heparin also decreases the incidence of left ventricular thrombi and is likely to have its greatest benefit in patients with large anterior infarctions where the incidences of mural thrombi and systemic emboli are highest.[69] In patients with small inferior infarctions, the adverse risks of heparin will be the same, but the benefits will be much smaller. Benefits and risks of heparin therapy for patients with anterior infarctions versus patients with inferior infarctions have not been presented as yet for either the GISSI-2/International Study or ISIS-3.

Stroke and disability: From the viewpoint of the patient, the etiology of the stroke, whether hemorrhagic or ischemic, is irrelevant. What is important is whether these patients survive and whether they are left with significant disability.

In large mortality trials, transient ischemic attacks lasting <24 hours have not been recorded routinely. Both the GISSI-2/International Study and ISIS-3 recorded the number of patients with disabling stroke and those who made a full recovery (data yet to be reported). In ISIS-2, 61 streptokinase-treated patients experienced stroke; 24 patients died (39%), 17 (28%) were disabled at discharge (degree of disability not classified), and 20 (33%) made a full recovery.[2] If the same frequencies are applied to the GISSI-2/International Study and ISIS-3, it is probable that of the 4 excess strokes per 1,000 patients noted with alteplase (duteplase) and anistreplase, 2 died and were already counted in the figures for total mortality, 1 patient survived with disability, and 1 patient made a full recovery. Therefore, the difference between the agents may be 1 disabling stroke per 1,000 patients treated.

Bleeding: Although bleeding and transfusion are undesirable and can be associated with morbidity, this is usually not the case in patients receiving thrombolytic therapy. Reduction of fibrinogen following thrombolytic therapy has not been related to bleeding risk.[70] Most often, bleeding is due to the lysis of hemostatic plugs formed at sites of previous vascular trauma; the incidence of systemic bleeding has usually been similar with the different agents (Table III). The incidence of bleeding relates to

TABLE III Major Bleeding (requiring transfusion) with Thrombolytic Therapy

Trial	Agent	Major Bleeding (%)
GISSI-1[1]	Streptokinase	0.3
ISIS-2[2]	Streptokinase	0.5
AIMS[3]	Anistreplase	0.8
ASSET[4]	Alteplase	0.2
GISSI-2/International Study[5]	Steptokinase	0.9
	Alteplase	0.6
ISIS-3[6]	Streptokinase	0.9
	Duteplase*	0.9
	Anistreplase	1.0

*Burroughs Wellcome supplied tissue plasminogen activator, duteplase.

AIMS = APSAC [Anisolated Plasminogen-Streptokinase Activator Complex] Intervention Mortality Study; ASSET = Anglo-Scandinavian Study of Early Thrombolysis; GISSI-1 = Grupo Italiano per lo Studio della Streptochinasi nell' Infarto Miocardico; GISSI-2 = Grupo Italiano per lo Studio della Soprovvivenza nell' Infarto Miocardico; ISIS = International Study of Infarct Survival (Second and Third).

how carefully bleeding is reported. In the GISSI-2/International Study there was an increase in major bleeding with streptokinase that has not been noted in other trials.[5] This finding may have been due to the unblinded nature of the comparison.

Allergy: Both streptokinase and anistreplase are foreign proteins and, therefore, risk of allergic reaction is associated with their use. However, the incidence of these reactions is low (Table IV). In ISIS-2, no cases of anaphylactic shock in 8,392 patients treated with streptokinase were reported.[2] In GISSI-2, although 7 of 5,860 patients treated with streptokinase developed anaphylactic shock, no deaths occurred.[1] Surprisingly in ISIS-3, there appeared to be more allergy with anistreplase than with streptokinase.[6] When repeat administration of a thrombolytic agent is required, alteplase (or urokinase, if available) should be given primarily because of concerns about the effectiveness of repeat administration.[71]

Hypotension: The mechanism behind hypotension associated with the infusion of thrombolytic agents remains unclear. However, thrombolytic-induced hypotension may be related to plasmin activation leading to the formation of bradykinin from kallikrein or activation of complement or endothelial prostacyclin secretion.[72] Hypotension is most common following rapid administration of streptokinase (Table V). However, anistreplase is also associated with hypotension; significant hypotension occasionally occurs with alteplase administration. In the European comparative trial of streptokinase and alteplase,[73] blood pressure fell below 90 mm Hg in 16% of patients treated with alteplase. In our comparative trial, 7.7% of alteplase-treated patients experienced a fall in systolic blood pressure to <80 mm Hg during the infusion.[7] When thrombolytic-induced hypotension occurs, administration of the agent may need to be interrupted. Supportive therapy such as postural measures and administration of intravenous fluids may help symptomatic patients. Severe hypotension may require pharmacological therapy.

TABLE IV Allergy Following Administration of Thrombolytic Agents

		Allergy (%)	
Trial	Agent	Minor	Major
GISSI-1[1]	Streptokinase	2.4	0.1
ISIS-2[2]	Streptokinase	4.4	0.2
AIMS[3]	Anistreplase	1.8	0.6
GISSI-2/International Study[5]	Streptokinase	—	1.7
ISIS-3[6]	Streptokinase	—	0.3
	Duteplase	—	0.1
	Anistreplase	—	0.6

See Table III for abbreviations.

TABLE V Hypotension Associated With Administration of Thrombolytic Agents

		Hypotension (%)	
Trial	Agent	Active	Control
GISSI-1[1]	Streptokinase	3.0	—
ISIS-2[2]	Streptokinase	10.0	2.0
AIMS[3]	Anistreplase	4.0	2.5
GISSI-2/International Study[5]	Alteplase	1.7	—
	Streptokinase	3.8	—
ISIS-3[6]	Streptokinase	6.8	—
	Duteplase	4.3	—
	Anistreplase	7.2	—

See Table III for abbreviations.

Reinfarction: Angiographic studies have shown a high rate of reocclusion of the reperfused infarct-related artery; however, reocclusion does not necessarily result in clinical reinfarction.[74] Following the use of aspirin, reinfarction rates have been low (Table VI). Reinfarction rates with anistreplase have been low compared with control even without the use of aspirin, as in the APSAC Intervention Mortality Study (AIMS).[3] In large, comparative studies, alteplase therapy has been associated with lower reinfarction rates than either anistreplase or streptokinase.[5,6] Theoretically, alteplase could lyse residual thrombi, which are potent stimuli for reocclusion, more effectively than the other 2 agents. However, even more likely, because higher reinfarction rates are usually associated with higher patency rates (more open arteries and therefore more are likely to close), is the possibility that the arteries opened early by alteplase also may have closed early because of the delayed heparin regimen (given subcutaneously either 4 or 12 hours after beginning alteplase).[9] Early closures of reperfused arteries could well be silent in the first 24 hours and, therefore, go undetected.

TABLE VI Incidence of Reinfarction in Trials of Thrombolytic Agents

		Reinfarction (%)	
Trial	Agent	Active	Control
GISSI-1[1]	Streptokinase	4.1	2.1
ISIS-2[2]	Streptokinase	2.8	2.4
AIMS[3]	Anistreplase	4.8	6.1
ASSET[4]	Alteplase	3.9	4.5
GISSI-2/International Study[5]	Alteplase	2.6	*
	Streptokinase	3.0	
ISIS-3[6]	Streptokinase	3.6	*
	Duteplase	3.1	*
	Anistreplase	3.8	

*$p < 0.01$; alteplase versus streptokinase, duteplase versus streptokinase and versus anistreplase.
See Table III for abbreviations.

BENEFIT-TO-RISK RATIO FOR INDIVIDUAL PATIENTS

Thrombolytic therapy with each of the available agents reduces mortality by approximately 25% in all subgroups, except for patients with ST-segment depression.[1-4] The absolute mortality reduction in each subgroup is dependent on baseline mortality for each group; benefit-to-risk ratios differ in different populations. Groups such as patients with hypotension (mortality approximately 35%), the elderly (>70 years; mortality approximately 22%), and patients with bundle branch block pattern (mortality approximately 25%) stand to gain the most from thrombolytic therapy.[2]

Patients at risk of bleeding, such as those with a previous stroke, previous gastrointestinal bleeding, or recent trauma, have the highest risk for adverse events. For individual patients, the benefit-to-risk ratio must be weighed. Unfortunately, there is a paucity of data with respect to benefit and risk in high-risk subgroups of patients (e.g., a patient in cardiogenic shock who has had a previous stroke).

In general, if the mortality for a particular group shown to benefit from thrombolytic therapy is >4%, a mortality reduction of 25% (10 lives saved per 1,000 patients treated) will approximate the risk of major bleeding of 1% and will be approximately 3 times the risk of hemorrhagic stroke if streptokinase is administered, and between 1.5 and 2 times the risk of hemorrhagic stroke if alteplase or anistreplase is given. Disabling stroke may not be increased by streptokinase but could be increased by 1 per 1,000 patients treated with the other 2 agents. Even in this situation, the benefit-to-risk ratio may be 10:1 (i.e., 10 lives saved for 1 disabling stroke), allowing that transfusion is not associated with significant morbidity. Additionally, long-term, thrombolytic therapy results in better prognosis and improved quality of life by preservation of left ventricular function.

ADJUNCTIVE THERAPY WITH HEPARIN

Sustained patency of the infarct-related artery is likely to be very important for achieving preservation of left ventricular function and improved survival.[9] Regimens of subcutaneous heparin given in ISIS-3 and in the GISSI-2/International trial (delayed either 4 or 12 hours) reduced mortality (by 5 patients per 1,000 treated) and reinfarction (by 3 patients per 1,000 treated) at a cost of 3 major bleeds per 1,000 patients and no increase in total stroke.[6] This regimen (12,500 U twice daily) does not significantly affect the activated partial thromboplastin time for about 36 hours,[69] and will have little effect on sustaining patency. In patency trials with alteplase and heparin (with or without a small dose of aspirin [80 mg]),[54,61] it seems that heparin is necessary to maintain early patency and alteplase to prevent reocclusion. Early intravenous heparin is also likely to be very beneficial with streptokinase and has been shown to improve the time to patency and to decrease infarct size in the absence of aspirin therapy.[75] Few data are available with respect to streptokinase, alteplase, or anistreplase and requirements for heparin therapy in the presence of adequate aspirin administration. Trials currently in progress will evaluate these requirements.

INDICATIONS FOR EACH AGENT

Given that thrombolytic agents are equally effective when given together with aspirin and delayed subcutaneous heparin, decisions as to which agent to use should be based on safety, cost, and familiarity. Streptokinase would seem to be the preferred agent for most clinical situations because it is the least costly. Alteplase has a special role when readministration of a thrombolytic agent is necessary in patients who have previously received either streptokinase or anistreplase.[71] It has been argued that alteplase should also be the agent of choice in patients with cardiogenic shock because of its rapid lysis and lower incidence of hypotension. However, results from ISIS-2 suggest that the incidence of hypotension with streptokinase was no higher in patients with initial systolic blood pressure <100 mm Hg than in patients with initial systolic blood pressure >150 mm Hg. Furthermore, in the GISSI-2/International Study, patients who presented in Killip class IV did better when treated with streptokinase.[5] Hospital mortality for streptokinase-treated patients was 64.9% versus 78.1% for alteplase-treated patients ($p = 0.014$).[5] Because alteplase has been shown to be a better agent for dissolution of old thrombi, patients presenting late are another group in which this agent may have a special role. However, no data are available to show that alteplase reduces mortality when given late, whereas there are supportive data with late administration of streptokinase.[2] Moreover, because the benefit-to-risk ratio is smaller for patients who are treated late, a less effective thrombolytic agent on old thrombi such as streptokinase, with a lesser likelihood of causing hemorrhagic stroke, may be preferred.

Anistreplase has an important advantage in ease of administration because it is given as a single bolus injection over 2–5 minutes. This enables the full thrombolytic dose to be given. As alteplase is infused over 3 hours, the infusion may be terminated because of the development of hypotension or arrhythmias, which may have nothing to do with the thrombolytic infusion. In ISIS-3, approximately 6% more patients received the full dose of anistreplase than received the full duteplase or streptokinase dose.[6] The prime aim of thrombolytic therapy is to lyse coronary artery thrombi to restore coronary blood flow. Possible side effects should be treated secondarily. Bolus administration of anistreplase may also be a distinct advantage for community administration where it may be difficult to maintain an intravenous line when moving the patient to the ambulance and during ambulance transport.

Each thrombolytic agent may therefore have particular indications. Adjunctive therapy regimens may optimally be different with each agent and ongoing trials will be necessary to improve on the substantial advance of thrombolytic therapy. The abiding principle is that a thrombolytic agent, no matter which one, should be given to most patients presenting with acute myocardial infarction.

In conclusion, the available thrombolytic agents are comparable in terms of clinical efficacy. However, differences exist among the agents in terms of safety and cost. Meta-analysis of approximately 90,000 patients randomized in thrombolytic trials worldwide will be very helpful in providing further information so as to enable evaluation of the safety profile of each agent. In addition, specific agents may have different indications for use. Thrombolytic (and antithrombotic) therapy should be tailored to the individual patient. The physician should keep in mind the benefits and risks in terms of short- and long-term mortality and the quality of life of the patient in terms of left ventricular dysfunction.

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Comparative Analysis of Long-Term Mortality After Thrombolytic Therapy

Keith A.A. Fox, MB, ChB, FRCP

In patients with acute myocardial infarction, thrombolytic therapy has a demonstrable and favorable impact on a range of clinical indicators, including left ventricular function, infarct size, coronary arterial patency, and symptom relief. However, these indicators have not provided a reliable basis for the comparison of thrombolytic regimens; mortality provides the "gold standard." One-year mortality obviates the differences in the timing of short-term comparisons (in-hospital, 30-day, or 5-week). In addition, late effects of differences in patency, including the impact of reocclusion, infarct healing, and remodeling, will be evident by 1 year. Meta-analysis of data from previous major mortality studies shows that differences in design and the overlap of confidence intervals of mortality studies suggest that no thrombolytic agent is superior in terms of short-term mortality. Long-term survival may provide a more meaningful basis for comparison of efficacy of the thrombolytic regimens. Long-term mortality has been evaluated for anistreplase in acute myocardial infarction in a composite analysis, similar to a meta-analysis. From the pooled life table analysis of all anistreplase studies, the odds reduction in mortality at 1 year was approximately 48%.

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The impact of coronary thrombolysis was dramatically evident during early experimental and clinical studies of intracoronary administration of thrombolytic agents. Recanalization of a previously occluded coronary artery produces dramatic and convincing visual evidence of efficacy.[1–3] Patency is restored to the occluded artery within minutes rather than the hours, or perhaps days, that are often required for endogenous recanalization. Thus, thrombolytic therapy accelerates recanalization; however, this is not necessarily equivalent to demonstrable clinical benefit.

In the development of thrombolytic therapy, numerous small-scale studies have failed to produce clear evidence of clinical benefit. A variety of clinical end points have been employed as indicators of efficacy in evaluating individual thrombolytic agents. End points have included the entirely subjective clinical responses of symptom relief, measures of electrocardiographic ST-segment resolution,[4,5] efflux of cardiac enzymes, global or regional ventricular function, infarct size, restoration of arterial patency, and mortality.[6–9] Sensitivity and specificity differ among the various end points that assess efficacy of the treatment of myocardial infarction, but results consistently favor thrombolytic therapy over placebo or conventional care. A meta-analysis provided some of the first convincing evidence that thrombolytic therapy may produce a significant mortality benefit.[10] The primary purpose of this article is to discuss why long-term mortality may be the most important indicator for evaluating the efficacy of thrombolytic therapy in patients with acute myocardial infarction.

CLINICAL END POINTS AS A SURROGATE FOR MORTALITY?

Infarct size: Estimates of infarct size, based on electrocardiographic criteria or efflux of cardiac enzymes, provide a clinical guide for thrombolytic efficacy.[4,5,9] However, these measures lack the sensitivity and specificity that is required for comparison of individual thrombolytic agents. More accurate

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quantitative measures of infarct size, for example, those employing positron emission tomography, are not always available to cardiologists.

Left ventricular function: Assessments of left ventricular function following thrombolytic therapy are often difficult to interpret because they are complicated by a number of confounding factors.[7] Estimates of global left ventricular function are insensitive because of compensatory hypercontractile function in normal myocardium and dyskinesis in ischemic tissue. In addition, arterial reperfusion results in reduced compliance of the affected myocardium, thereby influencing overall contractile measurements. These factors account for very modest differences (only 2–6%, absolute units) in global function in comparisons of thrombolysis with placebo treatment.[11]

Furthermore, both ischemia and irreversible myocardial injury may contribute to regional impairment of contractile function. Painstaking sequential studies are required to determine the recovery of functional capacity in ischemic muscle.

Delayed functional recovery, "stunned myocardium," follows transient ischemia, thereby confounding the interpretations of early studies. Detailed analyses of regional function are limited to centers with specialist expertise and interpretations are complicated by infarct healing. As proposed by White and colleagues,[12] providing an estimate of the extent of left ventricular dysfunction based on measurements of left ventricular systolic dimension may be possible. However, these estimations may also lack the sensitivity required for the comparison of individual thrombolytic agents.

Angiographic end points: Restoration of angiographic coronary arterial patency requires special attention. True "reperfusion" (restoration of arterial blood flow) studies are limited to those in which total coronary occlusion is demonstrated with a baseline angiogram. Furthermore, perfusion of myocardium is not necessarily equivalent to coronary arterial patency (open or unobstructed artery). Microvascular injury induced by ischemia and reperfusion may impair reperfusion despite a patent coronary artery. Because baseline angiograms have proved to be impractical for widespread application, coronary arterial patency has been adopted as a substitute. Studies adopting a patency end point include a proportion, perhaps 10–15%, of patients with incomplete occlusion of the affected vessel at the time of presentation. The Thrombolysis in Myocardial Infarction (TIMI) trial found a higher frequency of reperfusion with alteplase (tissue plasminogen activator [t-PA]) than with streptokinase when measured at 90 minutes,[13] but studies have revealed that there are no differences in patency when assessed later.[14] Thus, the interpretations and significance of angiographic studies are dependent on the timing of angiography. No convincing evidence has been put forward to suggest that 90-minute arterial patency provides an adequate basis for comparison of thrombolytic agents with respect to clinical outcome. Indeed, despite previously demonstrated differences in 90-minute patency, the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2) and International Mortality studies have failed to reveal a mortality benefit for alteplase or streptokinase in more than 20,000 patients.[15,16]

Although thrombolytic therapy has a favorable impact on a range of clinical end points including infarct size, left ventricular function, coronary arterial patency, and symptom relief, these indicators have not provided a reliable basis for the comparison of thrombolytic agents; mortality provides the "gold standard."

COMPARISONS OF SHORT- AND LONG-TERM MORTALITY

Meta-analysis of previously conducted major mortality studies suggests that, because of differences in design and the overlap of confidence intervals for short-term mortality, no thrombolytic agent is superior.[11] Long-term (≥1 year) survival may provide a more meaningful basis for comparison of the efficacy of thrombolytic regimens. One-year mortality obviates the differences in the timing of short-term comparisons. Timing in these comparisons varies from 2 (in-hospital analyses) to 5 weeks. In addition, late differences in patency (i.e., impact of reocclusion, infarct healing, and remodeling), are not revealed by short-term studies but are evident in long-term studies.

Rationale for meta-analysis: Although early small-scale studies involving streptokinase fail to reveal a significant mortality benefit when considered individually, a composite meta-analysis indicates an odds reduction of approximately 24%.[10,11] This reduction has correctly anticipated the results of the second International Study on Infarct Survival (ISIS-2) and Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI-1) trial.[17,18] Therefore, meta-analysis may provide a suitable method for comparison and evaluation of thrombolytic therapies.

The principles of meta-analysis have been established[11,19] and they can be summarized as follows:

TABLE I Effects of Intravenous Thrombolytic Agents on Early Mortality

Thrombolytic Agent (<6 hours after onset)	No.	Mortality (%) Active	Mortality (%) Control
Streptokinase	24,894	9.4	12.3
Alteplase	6,755	6.8	9.4
Anistreplase	2,315	6.1	11.0

Alteplase = tissue plasminogen activator (t-PA); Anistreplase = anisoylated plasminogen streptokinase activator complex (APSAC). (Modified from *Circulation*.[11,20])

Patients allocated to active treatment in one trial are compared directly only with controls in the same trial and not with patients in any other trial Therefore, differences in patient characteristics between trials are not relevant provided that the trials are broadly similar. This stratified approach compares "like with like" and is not affected by differences in patient characteristics among trials. For each trial, a number of events observed in the treated group is contrasted with the number of events that would have been expected had no treatment effect occurred. Random variations in individual trials, as a result of chance, are averaged out by the meta-analysis. The process does not assume that treatment has the same effect in the different trials, but rather that the effect will tend to be in the same direction in those trials. The process of performing a meta-analysis requires access to the original data, meticulous and unbiased extraction of data, and a comprehensive data base. A reliable overview of multiple trials should be based on a careful and exhaustive search for all trials conducted and a meticulous, unbiased extraction of data with the use of appropriate statistical methods.

COMPARISONS OF SHORT-TERM MORTALITY WITH DIFFERENT THROMBOLYTIC AGENTS

Held and colleagues[20] have conducted a meta-analysis of 8 randomized trials of alteplase and 10 of anistreplase (anisoylated plasminogen-streptokinase activator complex [APSAC]). The findings indicate that the odds of early death are reduced by 29% with alteplase and by 46% with anistreplase. However, 95% confidence intervals overlap, and, hence, investigators could not conclude that there was a significant difference in favor of either agent (Table I, Figure 1).[20] However, beneficial results from both agents were consistent and the findings were strengthened when all the trials were considered together. Similar results for streptokinase are included in Table I for comparison, as reported by Yusuf and colleagues.[11]

The Third International Study of Infarct Survival (ISIS-3): Preliminary results from the ISIS-3 study were presented at the annual meeting of the American College of Cardiology in March 1991.[21] This study involved 936 hospitals in 16 countries and the randomization of 46,092 patients. Patients with clear indications for thrombolysis were randomized to streptokinase, anistreplase, or duteplase (t-PA; Burroughs Wellcome) and aspirin alone (160 mg/day, chewed immediately) or aspirin plus subcutaneous heparin (12,500 U twice daily for 7 days, starting at 4 hours).

The findings revealed no significant differences in 5-week mortality (streptokinase 10.5%, duteplase 10.3%, anistreplase 10.6%). Similarly, there were no differences in the higher-risk subset of patients with ST elevation and presentation within 6 hours. The subcutaneous heparin regimen produced an insignificant trend toward lower mortality (for all

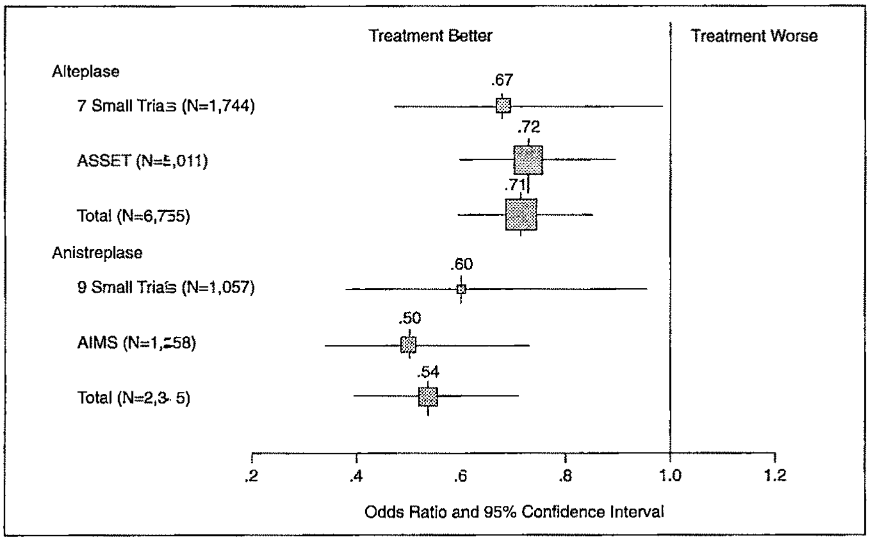

Figure 1. Meta-analysis of alteplase and anistreplase studies. A favorable trend is apparent for anistreplase, but the confidence intervals overlap with those of the alteplase studies. AIMS=APSAC Intervention Mortality Study; APSAC=anisoylated plasminogen–streptokinase activator complex; ASSET=Anglo-Scandinavian Study of Early Thrombolysis. (Modified with permission from *Circulation*.[20])

thrombolytics grouped together), but a significant excess of major bleeding episodes (3 per 1,000 patients treated), cerebral bleeding (2 per 1,000 patients treated), and a trend toward fewer reinfarctions (3 per 1,000 patients treated). Among patients treated with duteplase (with ST elevation and <6 hours duration), heparin reduced mortality (9% vs 10.1%). However, for streptokinase or anistreplase, the differences in mortality in patients receiving heparin (versus no heparin) with streptokinase or anistreplase were insignificant.

It may be inferred, therefore, that alteplase requires the graduated 3-hour infusion regimen followed by heparin; streptokinase requires the 1-hour infusion; and anistreplase requires a single injection. Although streptokinase and anistreplase may also benefit from the addition of heparin, this has not been convincingly shown. These simplified protocols have relevance for prehospital and emergency department thrombolytic administration. The definitive comparison of the 3 thrombolytic agents will be based on long-term mortality.

Early and late mortality results: A descriptive comparison of the influences of streptokinase, anistreplase, and alteplase on early and late mortality can be derived from the published results of the respective studies.[17,18,22,23] Figure 2 illustrates this comparison. However, this descriptive comparison does not necessarily compare "like with like," and, in particular, the entry criteria and timing differ among the illustrated studies. However, several important features emerge: first, all the studies reveal a consistent and important reduction in risk of death and a trend toward a lesser mortality reduction at the end of 1 year. In the APSAC Intervention Mortality Study (AIMS), the reduction in the risk of death was 50.5% (confidence interval 26.1–66.8%) for short-term analysis and 42.7% (confidence interval 20.9–58.5%) for the 1-year comparison. In GISSI-1, the short-term mortality reduction was 19% (for the 0–12-hour group) with confidence intervals of 1–28%. At 1 year, the reduction in the odds of death for the GISSI-1 study amounted to 10% (confidence interval 3–16%), and this range no longer overlaps that of the AIMS study. However, this observational comparison must be interpreted in the light of differences in study design and the fact that published information is not available for the time-stratified subsets of GISSI-1 and ISIS-2. An "AIMS equivalent" subset has been extracted from the ISIS-2 data base with an apparent mortality benefit of similar scale to that seen in AIMS.[11]

TABLE II Rationale for Comparisons of Long-Term (1-Year) Mortality

- Mortality end points avoid the problems that confound indirect clinical indications.
- One-year analyses incorporate the influence of late changes in vessel patency, infarct healing, and remodeling.
- One-year mortality provides a standard for the comparison of thrombolytic agents.

COMPOSITE ANALYSIS OF 1-YEAR SURVIVAL: ANISTREPLASE STUDIES

Comparisons of 1-year mortality may provide the standard for the comparison of thrombolytic agents (Table II). In order to determine whether the 1-year mortality results from the AIMS study are supported by all the studies fulfilling similar

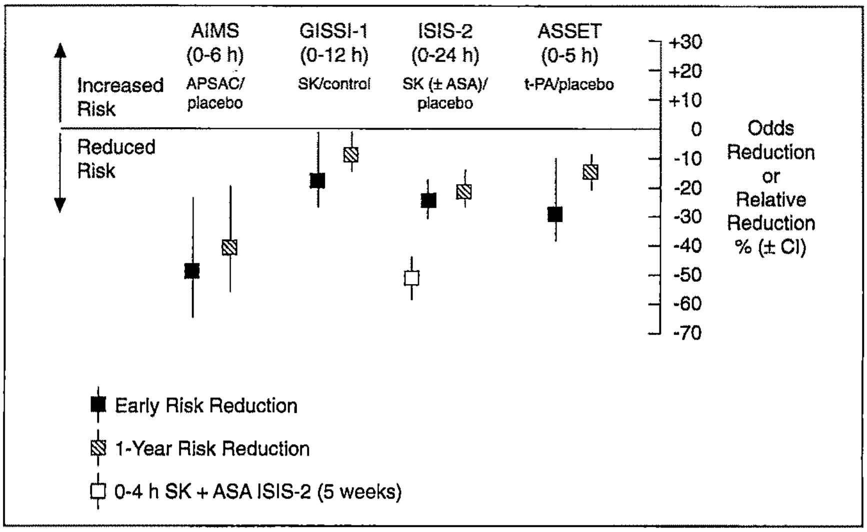

Figure 2. Observational comparison of early and 1-year mortality results for the 4 major studies. The studies differ with respect to entry criteria. In each case 1-year mortality shows a lower benefit than the early mortality result and the proportional change between 1-year and the early result is not equivalent for the 4 studies. The 0–4 hour subset of the Second International Study of Infarct Survival (ISIS-2) study shows results superior to those of the whole study and similar to the findings of the APSAC Intervention Mortality Study (AIMS). APSAC=anisoylated plasminogen-streptokinase activator complex; ASA=aspirin; ASSET=Anglo-Scandinavian Study of Early Thrombolysis; GISSI-1=Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico; SK=streptokinase.

TABLE III Pooled Analysis of Anistreplase Studies

Demographic Data	Anistreplase (n = 2,911)	Placebo (n = 634)
Age (%)		
≤60 y	62	63
≥61 y	37	36
Sex (%)		
Male	81	82
Female	19	18
History of AMI (%)		
Yes	12	18
No	88	82
Site of infarction (%)*		
Inferior	55	53
Anterior/both	45	47
History of angina (%)		
Yes	33	37
No	67	63
History of hypertension (%)		
Yes	17	18
No	83	82
Current smoker (%)		
Yes	63	66
No	37	34

*n = 1,895.
AMI = acute myocardial infarction.

entry criteria, a pooled analysis applying the principles of meta-analysis has been undertaken. Thrombolysis studies (published or unpublished) involving anistreplase treatment for acute myocardial infarction were included in this analysis. The studies include the AIMS (anistreplase vs placebo; double-blind randomized),[22] AIMS (nonrandomized; personal communication), Should We Intervene Following Thrombolysis? (SWIFT; intervention vs conservative therapy following anistreplase),[24,25] and the Brighton Study.[26] One-year mortality results and raw data were available for all studies. These studies required ECG evidence of myocardial infarction, treatment within 6 hours of symptom onset, 12 months follow-up, and assessment of mortality. Demographic data are provided in Table III; they confirm that subjects were well matched with respect to age and sex distribution, previous myocardial infarction, history of hypertension, smoking status, and site of infarction. A trend toward a lower frequency of prior myocardial infarction and angina was present in the active treatment group.

Life-table analysis: Life-table analysis reveals that 1-year mortality results from the AIMS double-blind published study are entirely consistent with the composite analysis for all studies. In the double-blind AIMS study, patients treated with anistreplase achieved an odds reduction in mortality of 42.7% (p=0.0007, 95% confidence intervals 20.9–58.5%).[22] This compares with an odds reduction of 47.9% for all anistreplase studies (p <0.0001; confidence interval 34.0–58.9%). Thus, 10.1% (294 of 2,910) of patients treated with anistreplase died at 1 year compared with 17.8% (113 of 634) of patients treated with placebo. Embarking on further placebo-controlled comparisons following the results of the AIMS study was not considered ethical; hence, placebo data are derived from the double-blind AIMS comparison[22] (Table IV, Figure 3).

Subgroup analyses: In the AIMS study, previously known ischemic heart disease (angina or infarction) was associated with increased mortality at 1 year (logistic regression analysis).[22] Composite analysis of anistreplase studies has confirmed these findings. Mortality rates increased approximately 2-fold in the presence of previous myocardial infarction, irrespective of anistreplase or placebo treatment. In the absence of previous myocardial infarction, 1-year mortality was 8.8% (225 of 2,556) with anistreplase and 15.8% (82 of 520) with placebo (48% odds reduction; confidence interval 31.7–60.4%). In the presence of previous myocardial infarction, the mortality rate was 19.9% (67 of 337 patients) for anistreplase and 27.4% (31 of 113 patients) for placebo (33.7% odds reduction; confidence interval, −8.5 to 59.5%).

Additional variables influencing 1-year survival included increased heart rate at presentation (>100 beats/min vs 51–59 beats/min), which resulted in a 92% increase in the odds of death (confidence interval, –168.9% to −37.3%). Previous angina was associated with an increase in the risk of death (36.8%; confidence interval, 19.0–50.8%). As demonstrated in the AIMS study, age was also an independent and powerful predictor, with 93% of

TABLE IV Anistreplase Pooled Analysis: Life-Table Analysis (AIMS Open Plus AIMS Double-Blind)*

Mortality	AIMS Double-Blind	AIMS Open/Double-Blind	Pooled Data
Anistreplase (%)	69/624 (11)	171/1,588 (10.8)	294/2,910 (10.1)
Placebo (%)	113/634 (17.8)	113/634 (17.8)	113/634 (17.8)
Odds reduction (%)	43†	44‡	47.9‡
95% CI	21.0, 59.0	27.5, 56.7	34.0, 58.9

*These data support the findings of the AIMS double-blind study. Very similar treatment and placebo mortality figures are obtained with the similar odds reduction in the risk of death.
†p = 0.0007.
‡p = 0.0001.
AIMS = APSAC Intervention Mortality Study; APSAC = anisoylated plasminogen activator complex; CI = confidence interval.

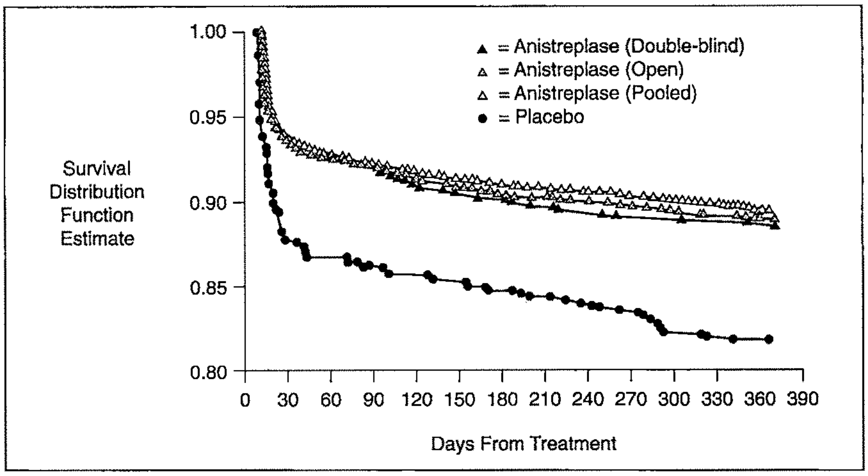

Figure 3. The survival curves demonstrate that the results of the APSAC Intervention Mortality Study (AIMS) double-blind, AIMS open, and the pooled analysis are virtually superimposable, thus supporting the findings of the AIMS study. APSAC=anisoylated plasminogen-streptokinase activator complex. (Adapted with permission from *Lancet*.[22])

patients <60 years of age surviving up to 1 year compared with 82% of patients ≥ 60 years of age. The following characteristics were not demonstrated to be independent predictors of survival: gender, history of hypertension, history of smoking, and time to administration. Among the entire data set of 3,545 patients, only 157 were treated within the first hour. This represents $<5\%$ of the total and provides an insufficient basis to resolve the question of additional benefit from very early treatment.

INTERVENTION STUDIES

Criteria for inclusion or exclusion in a study may have a profound influence on mortality rates within that study. Thus, caution must be exercised when comparisons are made between studies requiring angiography and invasive procedures with those not requiring such interventions. However, comparisons of interventional studies of similar design can be undertaken, and in this context the TIMI-IIB Study (alteplase) and the SWIFT study (anistreplase) have very similar design characteristics.[24,25,27] An analysis has also been undertaken of a composite of the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) studies with similar entry criteria.[28] Table V summarizes the findings from these three studies. Remarkably, 1-year mortality figures are very similar for the intervention groups and conservative group, irrespective of the thrombolytic agent.

TABLE V Comparison of Intervention Studies*

		One-Year Mortality (%)	
Trial	No.	Intervention	Conservative
TIMI-IIB (alteplase)	1,681	7.0	7.6
SWIFT (anistreplase)	800	5.8	5.0
TAMI Composite (alteplase, 6 studies)	847	6.1	5.9

*Comparison of intervention studies of similar design reveals almost identical 1-year mortality figures, irrespective of the thrombolytic agent. The differences in mortality results between intervention studies and conservative studies may be a reflection of selection criteria.

SWIFT = Should We Intervene Following Thrombolysis?; TAMI = Thrombolysis and Angioplasty in Myocardial Infarction; TIMI = Thrombolysis in Myocardial Infarction.

These figures are also very similar to 1-year mortality for the medium-risk group from the AIMS study.[22] In AIMS, the low-risk group had a 4.8% mortality at 1 year for active treatment and 7.9% for placebo. The medium-risk group had an 8.5% active treatment mortality and 12.4% placebo mortality and the high-risk group 18.4% active treatment and 33.5% placebo treatment at 1 year.[22]

CONCLUSION

Mortality benefits of thrombolytic therapy are not necessarily predictable based on clinical indicators, including vascular patency and mechanical function. The composite analysis of APSAC studies has reinforced the findings of the published AIMS double-blind study, with strikingly similar mortality findings at 1 year and almost identical risks in the odds of death (48%). Comparisons of studies of similar design, involving interventional procedures, such as angiography and angioplasty, have revealed strikingly similar 1-year mortality results with anistreplase and alteplase. Furthermore, the findings reveal that apparently low mortality figures associated with interventional studies may be a function of patient selection, because interstudy differences disappear when entry criteria are very similar. Mortality end points avoid the problems that confound indirect clinical indicators. One-year mortality provides a standard for the comparison of thrombolytic agents and incorporates the influence of late changes in vessel patency, infarct healing, and remodeling.

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Roundtable Discussion

Dr. Joseph Alpert (Worcester, Massachusetts): Because early (90-minute) patency does not appear to predict the outcome of patients with acute myocardial infarction, should angiography be performed later in the course of treatment (≥ 1 day) to assess patency?

Dr. Jeffrey Anderson (Salt Lake City, Utah): In the Third Trial of Eminase in Acute Myocardial Infarction (TEAM-3) study, angiography was performed to assess patency at 1 day rather than at 90 minutes. By 1 day, the patency rates for anistreplase and alteplase were 85–90%. I think that angiography performed later, at about 1 day, may provide a useful and still relatively early 'plateau' patency rate, which may be predictive of relative clinical outcomes. However, this will require further study.

Dr. Alpert: Should all patients with acute myocardial infarction have initial angiography performed, or should they have this procedure 2–3 days post-thrombolytic therapy, if at all?

Dr. Peter Sleight (Oxford, England): I certainly would not have an angiogram on myself on day 1 if I did not feel I needed it. This has been explored many times, and I think the best approach is to be guided by the clinical situation. If a patient has continued stuttering pain, then an angiogram should be obtained. Additionally, if the patient has active ischemia after getting out of bed or after exercising, then an angiogram becomes a necessary diagnostic tool.

Dr. Elliot Rapaport (San Francisco, California): If a patient presents early after symptom onset and contraindication to the use of thrombolytic therapy exists, then immediate angiography and primary angioplasty are appropriate. In my view, this situation is the only indication for primary angioplasty in treating acute myocardial infarction.

Dr. Alpert: Can thrombolytic agents be given to patients currently taking anticoagulants?

Dr. Sleight: Yes, there is more risk of bleeding in patients already taking anticoagulants. However, full-dose intravenous heparin is commonly used with all thrombolytic agents, although some prefer to administer heparin at the end of the thrombolytic infusion.

Dr. Alpert: There are various anticoagulant regimens, some intravenous and some subcutaneous, for use with the different thrombolytic agents. In other words, if a patient receives alteplase, should he or she receive a specific (intravenous) anticoagulant regimen? Also, if the patient receives anistreplase or streptokinase, should he or she receive a different anticoagulant regimen?

Dr. Rapaport: There really has been no trial comparing the combination of intravenous heparin and a thrombolytic agent to subcutaneous heparin and a thrombolytic agent in patients with acute myocardial infarction. Perhaps the intravenous-heparin group will be able to be compared with the subcutaneous-heparin group in ISIS-3 to see whether there was an increased risk of bleeding in this situation.

Dr. Sleight: We have no scientifically concrete evidence that heparin regimens must be different with the different thrombolytic agents. In the ISIS-3 subgroup analysis of 3,000 patients who received intravenous heparin (a nonrandomized comparison) and a thrombolytic agent, there was absolutely no difference between duteplase and streptokinase in mortality rates; therefore, giving intravenous heparin certainly did not favor duteplase mortality, as many would have thought. Also, there were no differences in reinfarction in patients receiving duteplase or streptokinase with intravenous heparin, and the incidence of stroke in patients receiving intravenous heparin and a thrombolytic was about twice that observed in patients receiving subcutaneous heparin and a thrombolytic. We must question whether intravenous heparin has been adequately tested for risk and benefit. It has mostly been tested in patency studies, not in large studies of high-risk patients.

Prof. Keith Fox (Edinburgh, Scotland): There were comments about the increased risk of cerebral bleeding seen in ISIS-3 with duteplase and anistreplase compared with streptokinase and the reduction in reinfarction with duteplase compared with streptokinase and anistreplase. We might actually argue that less intensive anticoagulation would be better with streptokinase and anistreplase, but more intensive with duteplase (or alteplase), which has been the prior view. On the other hand, intensive anticoagulation may be more adverse, given the higher risk of cerebral bleeding observed in ISIS-3 in patients receiving duteplase and intravenous heparin.

Dr. Alpert: Dr. Fox, are there any data in the pooled analysis reflecting which anticoagulant regimen to use?

Prof. Fox: There are not; however, information from ISIS-3 suggests to me that there may well be differences with respect to the thrombolytic agents. Nonetheless further analysis is needed before definitive conclusions can be reached.

Dr. Alpert: Dr. Bassand, are allergic reactions more common with anistreplase than with alteplase?

Dr. J. P. Bassand (Besançon, France): In our last trial in which anistreplase and alteplase were compared, there was no significant difference in the incidence of allergic reaction or cutaneous rash during the first few hours of therapy between the 2 study groups. However, in other trials, such as ISIS-3, the incidence of allergy was greater with anistreplase.

Dr. Alpert: Can we come to a consensus regarding a dose of aspirin that should be used as an adjunct to thrombolytic therapy?

Dr. Bassand: In our institution, we usually give 250 mg of aspirin.

Dr. Rapaport: The low doses of aspirin (80 mg) used in the Heparin Aspirin Reinfarction Trial (HART) are not appropriate in the setting of acute myocardial infarction. A more appropriate dosage is either 325 mg swallowed, or 160 mg of aspirin chewed, although I am not sure if there is much difference between the 2 regimens. Results from ISIS-3 demonstrated that 160 mg was an effective dose, and that seems reasonable.

Prof. Fox: In ISIS-2, although there was a time-stratified benefit for the thrombolytic agent, there was no time-stratified benefit for aspirin. This suggests that the kind of aspirin doses we are talking about, ≥150 mg, are appropriate. However, evidence concerning early administration of aspirin is actually weak evidence.

Dr. Sleight: I disagree with you, Dr. Fox. I think that there is equal benefit from aspirin, whenever you administer it. Aspirin is an emergency medicine. I recommend when physicians see a patient with unstable angina and are able to render a diagnosis quickly, give the patient an aspirin to chew while the rest of the history is obtained.

Dr. Anderson: Our group uses the former 'baby aspirin,' which is no longer used in infants or children because of Reye's syndrome. However, for adults, this low-dose (80 mg) aspirin is easy to administer, flavored, palatable, and easy and pleasant to chew. Initially, we have our patients chew 2 of these tablets (160 mg of aspirin). Then, because of convenience in the United States, our patients receive 1 (325 mg) enteric-coated aspirin daily.

Dr. Rory Collins (Oxford, England): In the acute stage of myocardial infarction, an aspirin dose of at least 120–160 mg should be given. It would not be irrational to give slightly more than 160 mg as the first dose, as was shown to work in ISIS-2, and then to continue with 160 mg.

Dr. Alpert: Given the state of our incomplete knowledge about thrombolysis, is there any reason to select one thrombolytic agent over another for the 'average' patient with acute myocardial infarction?

Dr. Bassand: Urokinase or alteplase should be used in patients who previously received streptokinase or anistreplase, because the rapid increase in the level of antistreptokinase antibodies prevents any thrombolytic action when either streptokinase or anistreplase is reinjected. Except in this particular case, I do not see any evidence to choose one thrombolytic agent over another. In our institution, within the last 2–3 years, anistreplase or alteplase was preferably given to patients with anterior-wall infarction because these agents were thought to produce higher patency rates.

Prof. Fox: A key issue involves the proportion of patients who are eligible for thrombolytic therapy. Previous reviews performed in the United States indicate that a very small proportion of patients are currently being treated. In our center and in a number of others in Great Britain, approximately 55% of patients with acute myocardial infarction are currently being treated. However, this would argue for the simplest regimen possible, whether this be bolus administration of anistreplase or alteplase. Bolus administration may confer convenient advantages, but there may not be a mortality advantage.

Dr. Anderson: Cardiologists in our institution have gone on the assumption, to date, that all thrombolytic agents are probably equal, and we have treated patients with all of them. Data from ISIS-3 seem to confirm that all of our patients have been well served. The issues of cost, safety, and convenience continue to be issues for the future. I think the cost issues are clear, and the safety issues are becoming more interesting. Based on data from GISSI-2, streptokinase may be safer than alteplase in patients > 70 years of age. Data from ISIS-3 may further help to determine whether one agent is clearly safer than another in particular subgroups. With respect to convenience, I think anistreplase has a major advantage. When I write an order for alteplase or streptokinase, I do not know if it has been given, unless I come back 1–2 hours later. A physician can draw up and personally administer anistreplase in approximately 5 minutes. In my view, personally ensuring that the thrombolytic is given immediately and is in the circulation is an advantage of anistreplase.

Dr. Sleight: We use streptokinase in most patients with first-time infarcts. For second-time infarcts, within perhaps 6–12 months after previously receiving streptokinase or anistreplase, we use alteplase.

Dr. Harvey White (Auckland, New Zealand): Generally, I use streptokinase because it is the most economical thrombolytic agent, and it has the advantage of convenience and rapid administration. Even in the hospital, there is an advantage in the emergency department to get the drug into the circulation before the patient gets to the coronary care unit. The aim is to get the drug into the patient and then treat the side effects. Alteplase is more expensive, and I would reserve it for readministration to patients previously treated with streptokinase or anistreplase.

Dr. Alpert: We have learned a great deal from this discussion. Some of the key points include performing angiography at 1 day, rather than at 90 minutes following thrombolytic therapy, or as the clinical situation demands, to assess patency and reperfusion; considering angioplasty in patients who have contraindications to thrombolytic therapy; and administering thrombolytic agents to patients who are currently taking anticoagulants only if sufficient clotting is observed. Additionally, aspirin (approximately 160 mg) should be given immediately, as an adjunct to thrombolysis, to patients presenting with symptoms of acute myocardial infarction.

The panel agreed that the available thrombolytic agents are equally effective for the treatment of acute myocardial infarction. In terms of efficacy, there is no reason to use one agent over another. However, allergic reactions, although generally not serious, are observed more commonly in patients who receive streptokinase or anistreplase. Thus, in patients who have previously received streptokinase or anistreplase, alteplase may be the preferred thrombolytic agent. Other points to consider include cost and ease of administration. Streptokinase is the most economical thrombolytic agent, yet anistreplase is the easiest (a single bolus injection) and quickest (over 2–5 minutes) thrombolytic agent to administer.

Summary

Joseph S. Alpert, MD

The benefits of thrombolytic therapy clearly outweigh the risks. In general, these benefits include decreased mortality and improved left ventricular function. End points of thrombolytic therapy, such as patency, reocclusion, left ventricular function, reinfarction, stroke, and mortality, are substantially improved in patients who have received a thrombolytic agent compared with those who have not. Which thrombolytic agent is best among the 4 that are available? The answer depends, of course, on how one defines "best."

To define the best thrombolytic agent, the end points of therapy must be examined. Mortality is obviously the critical factor. Ideally, our patients should be sent home alive and without serious hemorrhage or disability. Cost and ease of administration are also major factors to be considered, particularly because resultant patency, reperfusion, and mortality appear to be similar among currently available drugs. Which thrombolytic agent is best? Streptokinase, alteplase, and anistreplase are equally effective in producing rapid thrombolysis and reducing mortality; therefore, the clinical situation may dictate which agent is preferred. For example, because of the potential for allergic reaction, patients who have recently received streptokinase or anistreplase should receive urokinase or alteplase if readministration is necessary. Anistreplase may be the ideal agent for community use, given its simple and rapid administration protocol. Other questions that have not been raised or adequately studied, at least in trials to date, include functional class, return to work, and cost.

We should not only be asking, "What is the best thrombolytic?" but also, "What is the best thrombolytic regimen?" More attention should be given to adjunctive anticoagulant therapy and other adjunctive therapy, such as β blockers, calcium antagonists, or nitrates. Various subgroup analyses from the Third International Study on Infarct Survival (ISIS-3) and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2) may provide insight into heparin administration. New thrombolytic regimens that could potentially improve product safety need to be evaluated. Indeed, fascinating preliminary information suggests that there are differences in complications and mortality related to alterations in the timing of drug administration. Further study in the area of prehospital administration of these agents is required and attention must be focused on treating as many patients as possible to reduce mortality. All of this is grist for further study and discussion. Thrombolytic therapy will be an area of great interest to cardiologists well into the next decade.